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Derivatives of Thiazoles, Triazoles, Thio- And Semi carbazones Show Promise as New Drugs for Treating Tuberculosis

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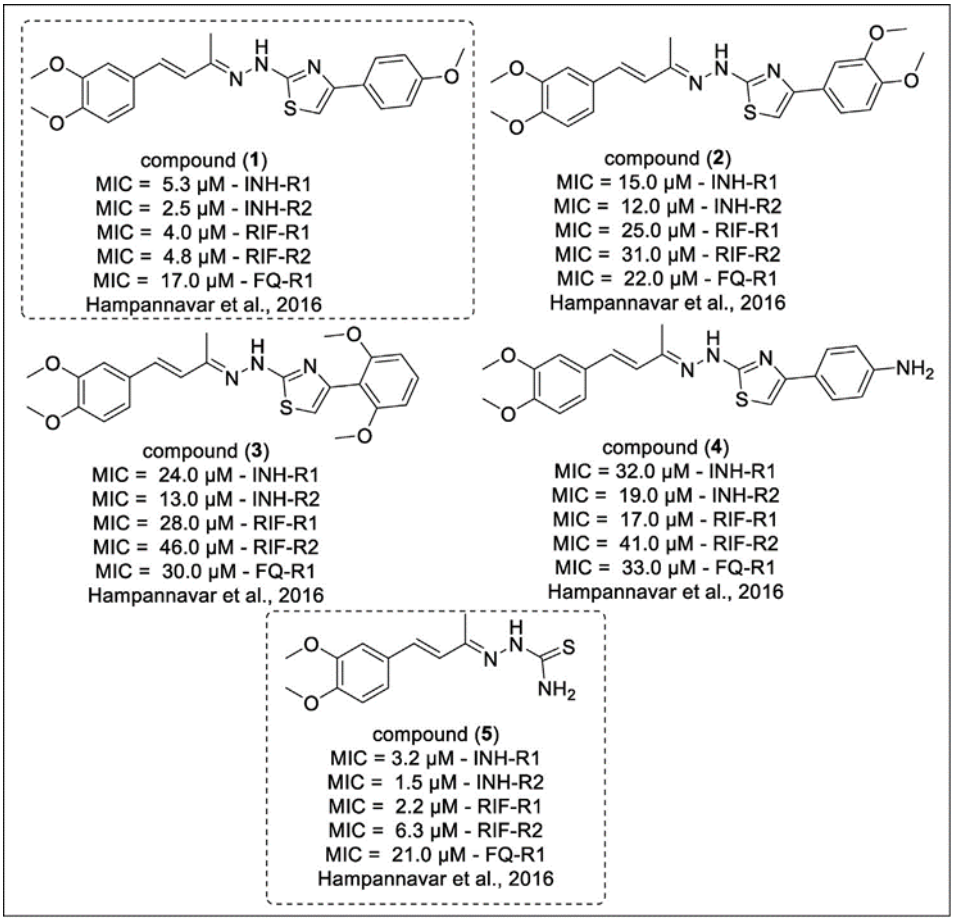
ABSTRACT

The favored motifs thiazole, triazole, thio, and semi carbazones serve as pharmacophores in bioactive molecules for various ailments, including tuberculosis (TB). Infectious disease tuberculosis (TB), which is mainly brought on by Mycobacterium tuberculosis, caused 4,000 fatalities every day in the world in 2013. The gradual decline in TB infections is primarily due to drug resistance and a lack of innovative treatments. This review article examines recent developments in developing anti-TB medications using thiazole, triazole, thio, and semi carbazone scaffolds. Beyond these current trends, we show the efficacy of the thiazole, triazole, thio, and semi carbazone strategy in the anti-M-tuberculosis drug development field of medicinal chemistry.

INTRODUCTION

Although there are many bioactive substances, it is well known that thiazole, triazole, thiosemicarbazone, and semi-carbazone conjugates have a wide range of pharmacological effects, including antioxidant antiproliferative, antiparasitic, anti-bacterial, anti-inflammatory, analgesic, neuroprotective, and anti-thiazole, triazole, and thiosemicarbazone derivatives are lead structures for the investigation of structure-activity relationships to promote to improve physical chemical proprieties, and, consequently, decrease their cytotoxicity effect and increase their anti-TB activity, particularly against resistant Mycobacterium tuberculosis (Mtb) strains. These factors make these pharmacophore groups advantageous.

This review paper will summarize the current situation using thorough and organized literature reviews of thiazole, triazole, thiosemicarbazone, and semicarbazone-based compounds with anti-TB efficacy. To support the claims of thiazole, triazole, and thiosemicarbazone and semicarbazone-based analogs for drug design, however, detailed studies on antiproliferative activities against various human cancer cell lines, gram-negative and gram-positive bacteria, kinetoplastid parasites, cytotoxicity assay against normal cells, animal models (in vivo experiment in fish and mice), biodistribution parameters, as well as probable mechanisms of action of Only molecules published in the recent ten years (2011–2014) in the databases Springer, Scopus, Science Direct, PubMed, Wiley, American Chemical Society, and the Web of Science were included in our description of the newest compounds. Thiazole, triazole, and Mycobacterium tuberculosis were the search terms utilized for this review, as well as thiosemicarbazone/semicarbazone and Mycobacterium tuberculosis. A total of 2611 articles were screened out after reading the title and abstract for this manuscript, including 957 articles on thiazoles and Mycobacterium tuberculosis, 1323 articles on triazoles and Mycobacterium tuberculosis, and 331 articles on thiosemicarbazone/semicarbazone and Mycobacterium tuberculosis (482 articles were excluded after full-text review studies conducted before 2011).



In addition, 2129 full-text articles from the 2011–2014 period were evaluated for eligibility, but 2100 articles were excluded after full-text reviews of 790 articles on thiazole and Mycobacterium tuberculosis, 1110 articles on triazole and Mycobacterium tuberculosis, and 229 articles on thiosemicarbazone/semicarbazone and Mycobacterium tuberculosis. As a result, 29 new research were included in this review, including five articles on thiosemicarbazone, 14 on triazole and Mycobacterium tuberculosis, and 10 on thiazole and the disease.

Tuberculosis

Mycobacterium tuberculosis is the primary cause of tuberculosis (TB), an infectious illness that claimed 1.4 million lives globally in 2013, or 4,000 per day. For decades, TB has consistently ranked among the top 10 infectious disease killers in low- and middle-income nations.

One of the significant risks to modern development, food security, and global health is antibiotic resistance. Anyone, regardless of age or location, can be impacted. One method of preventing the spread of TB is through TB resistance or the TB resistance solution. Globally, only 57% of MDR/RR-TB patients complete their treatments successfully. The most recent modification to the definition of TB resistance reads Multi-Drug-Resistant-TB (MDR-TB): Resistance to at least isoniazid and rifampicin, the two main drugs used to treat TB. Like MDR-TB, rifampicin-resistant tuberculosis (RR-TB) needs clinical care.

The condition known as pre-extensively drug-resistant tuberculosis (Pre-XDR-TB) satisfies the criteria for multidrug-resistant and rifampicin-resistant tuberculosis (MDR/RR-TB). It is also resistant to fluoroquinolone. Strains that fit the criteria for MDR/RR-TB and are also resistant to any fluoroquinolone and at least one additional follow-up medication, such as levofloxacin, moxifloxacin, bedaquiline, and linezolid, are the source of XDR-TB. Resistant TB treatment will require daily doses for more than two years, whereas susceptible TB treatment takes six months and has a 70% efficacy rate.

Anti-TB substances with a thiazole base

A thiazole is a crucial component in medicinal chemistry with many biological actions, particularly antiproliferative properties. Four novel styryl hydrazine thiazole hybrids (1-4) and their thiosemicarbazone-intermediary derivative (5, Fig. 1) were discovered by Hampannavar and colleagues in 2010. Therefore, these compounds (1-5) were assessed with anti-TB effect against five resistant clinical Mtb strains, including INH-R1 (Y155), INH-R2 (ATCC35822), RIF-R1 (S522L), RIF-R2 (ATCC35828), FQ-R1 (fluoroquinolone-resistant strain-D94 N), where INH is isoniazid, RIF is rifampicin and FQ is Fluoroquinolone [91]. As a result, the MIC values for compounds (1–

5) varied from 3.2 to 32 M (INH–R1), 1.5–19 M (INH–R2), 2.2–28 M (RIF–R1), 4.8–46 M (RIF–R2), and 17–33 M (FQ–R1).

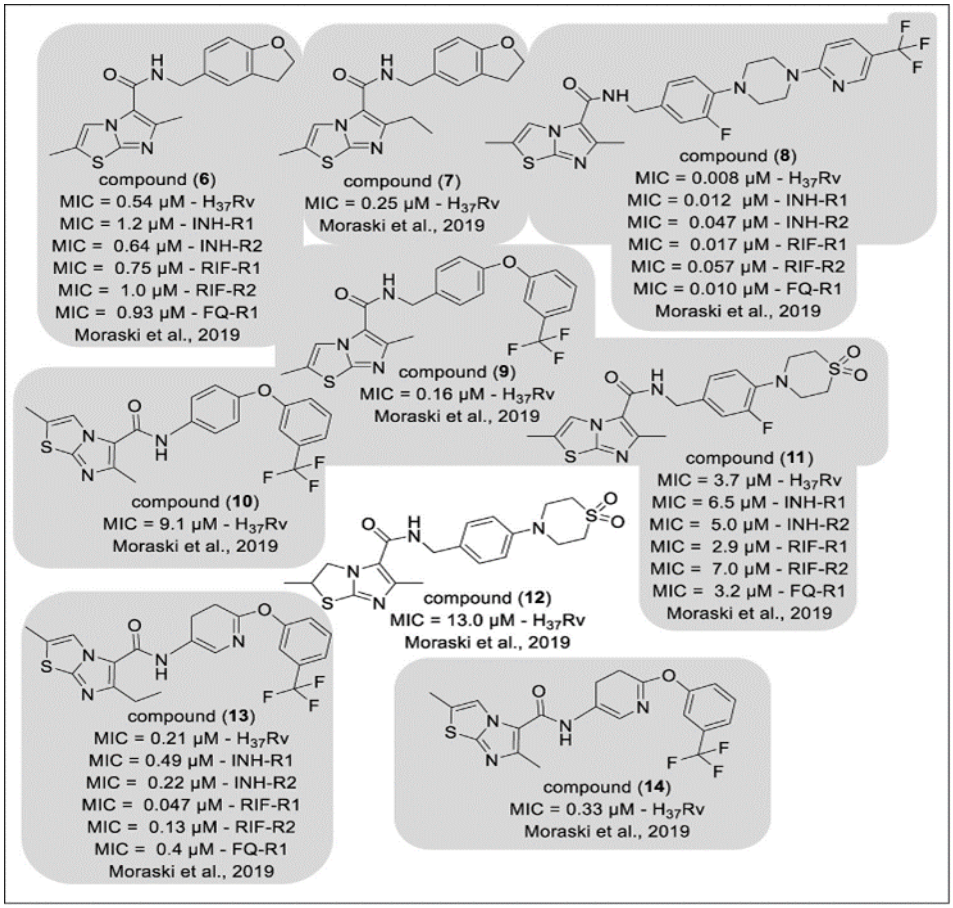


Fig. 2. Maraski et al. (2014) displayed nine new imidazo [2,1-b]thiazole-5-carboxamide derivatives (6-14).

Moraski et al. (2014) demonstrated the efficiency of nine novel imidazo [2,1-b]thiazole-5carboxamide derivatives against Mtb (H37Rv - ATCC 27294) (Fig. 2). When their cytotoxicity (CC50) against VERO cells (ATCC CCL81) was evaluated, CC50 values > 50.0 M were found (6–14). The MIC values for these drugs' anti-TB activity against the H37Rv strain were 0.008–13 M (Fig. 2). It is worth mentioning that analogs (6, 8, 11, and 13) presented potent efficacy against five different resistant clinical isolates Mtb strains with MIC range between 0.012 and 6.5 µM (INH-R1), 0.0047-5.0 µM (INH-R2), 0.0017-2.9 µM (RIF-R1), 0.0057-7.0 µM (RIF-R2), and 0.010-3.2 µM (FQ-R1) (Fig. 2). The compound (8) underwent an ADME examination utilizing hepatic microsomes, which revealed a half-life of 28.4 min. This chemical (8) was assessed in vivo for its safety and anti-anti-TB activity. As a result, this substance was not hazardous at large doses (>500 mg/kg-1), and after 30 treatment days (five days/week - 200 mg/kg-1), it was able to diminish the colony-forming unit in the lung and spleen. However, no statistically significant changes existed between the chronic TB stage and the control group.

With a mild anti-TB action (H37Rv-ATCC 27294), Eroglu and associates (2014) synthesized and studied 12 novel thiazolidinone-azole analogs (15–26). The MIC values for these substances (15–26) ranged from 14.27 to 155.76 M (Fig. 3). A series of aryl carboxamide derivatives were displayed by Alsayed et al. (2014), revealing three thiazole analogs (27–29) with anti-TB action (H37Rv-ATCC 27294). The substances (27) and (29) had moderate MIC values of 32 g/mL1 (85.81 M) and more, respectively. Compound (28) displayed an excellent MIC range of 4 g/mL1 (9.82 M, Fig. 4), while the other two compounds did not (>77.39 M), respectively.

A benzothiazole derivative (30) with activity against Mtb (H37Rv - ATCC 27294), Mycobacterium smegmatis (M. smegmatis), and Mycobacterium bovis BCG (M. bovis) was discovered by Wang and coworkers in 2013. This substance (30) was also considered anti-Escherichia coli, Staphylococcus aureus, and Pseudomonas aeruginosa. As a result, compound (30) gave Mtb and M MIC values of 0.19, 4.5, and 3.0 g/mL-1. as well as M. In contrast, bovis (Fig. 5). The down-regulation of persistence genes, inhibition of cell membrane synthesis, and inhibition of the molybdenum cofactor (Moco) production pathway were used to identify its likely mechanism of action. The drug (30) was also tested in acute and chronic TB murine models with five daily doses (40 mg/kg-1 and 100 mg/kg-1). It showed the ability to reduce the splenic and hepatic colony-forming unit in both stages of TB infection.

Additionally, the substance (30) demonstrated efficacy against both gram-positive and gram-negative bacteria, with MIC values > 7.5 g/mL-1 against E. coli, S. aeruginosa, and S. aureus. Five novel thiazole and benzothiazole compounds (31-35) were synthesized by Chandrasekera and colleagues in a series in 2014. The effectiveness of these compounds (31-35) against Mtb (H37Rv - ATCC 27294) and Vero cell lines was next evaluated; results revealed MIC values between 9 and >20 M and low selective index (SI) of 0.05-0.2 due to high cytotoxicity with CC50 ranges from 1.0 to 3.0 M (Fig. 6).

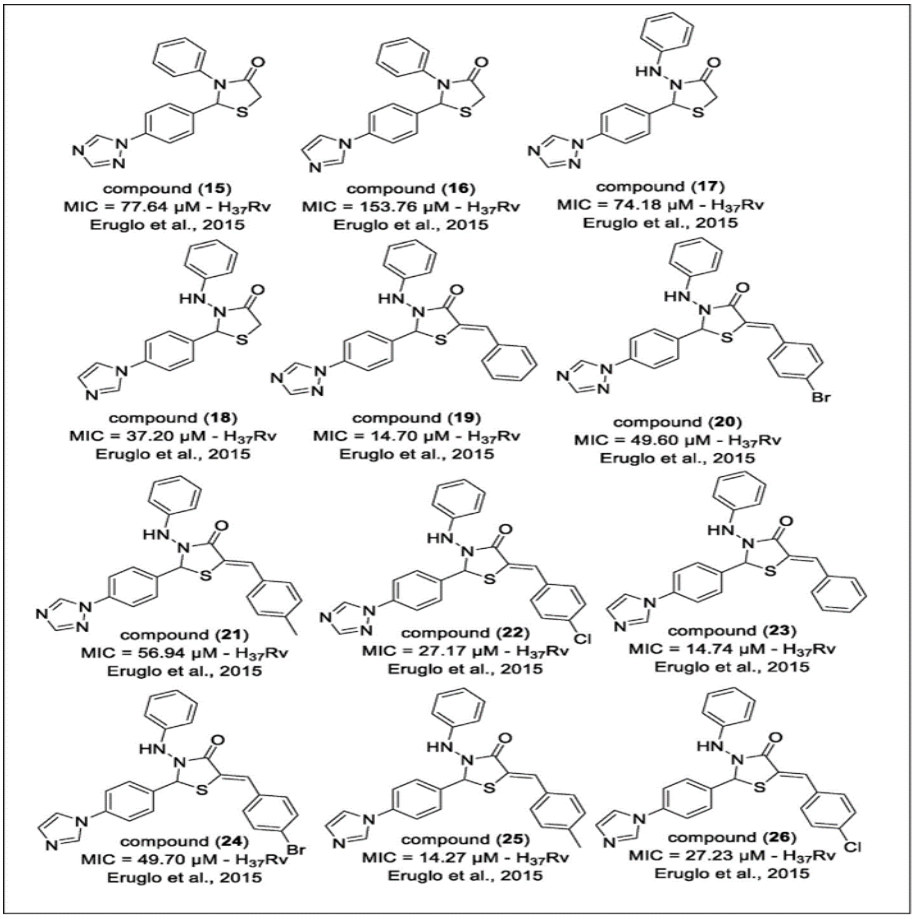


Fig. 3. By Eroglu et al. (2014), new thiazolidinedione-azole derivatives (15–26) were demonstrated.

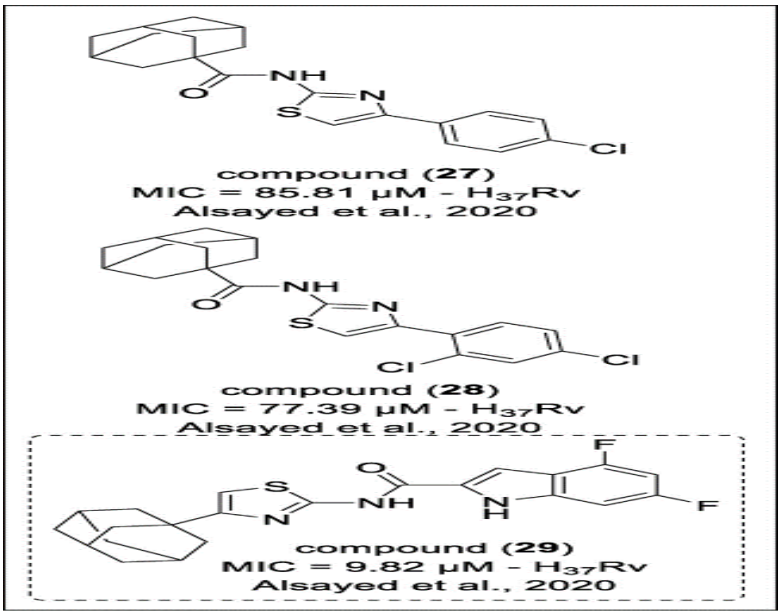


Fig. 4. By Alsayed et al. (2014), three brand-new aryl carboxamide-thiazole derivatives (27–29) were displayed.

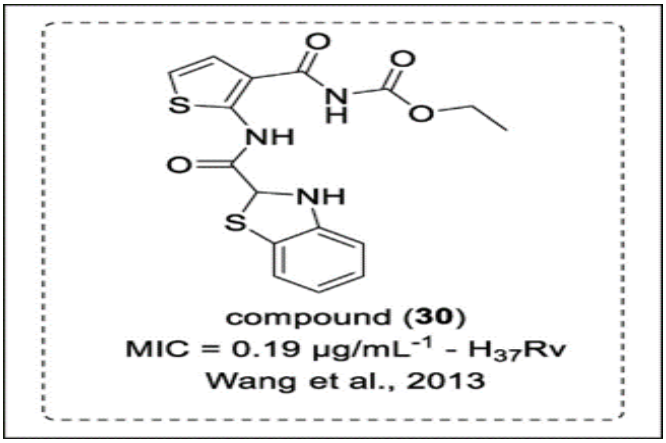


Fig. 5. Wang et al. (2013) demonstrated a new benzothiazole analog (30).

Six new imidazo[2,1- b] thiazole analogs (36-41) with anti-TB (H37Rv-ATCC 27294) and antiviral (Feline coronavirus and Feline herpesvirus) actions have recently been discovered by Gürsoy and associates (2014) [97]. Three substances showed a potent MIC range of 4.5 g/mL1 (8.4 M), 1.4 g/mL1 (1.5 M), and 0.7 g/mL1 (0.8 M), respectively.

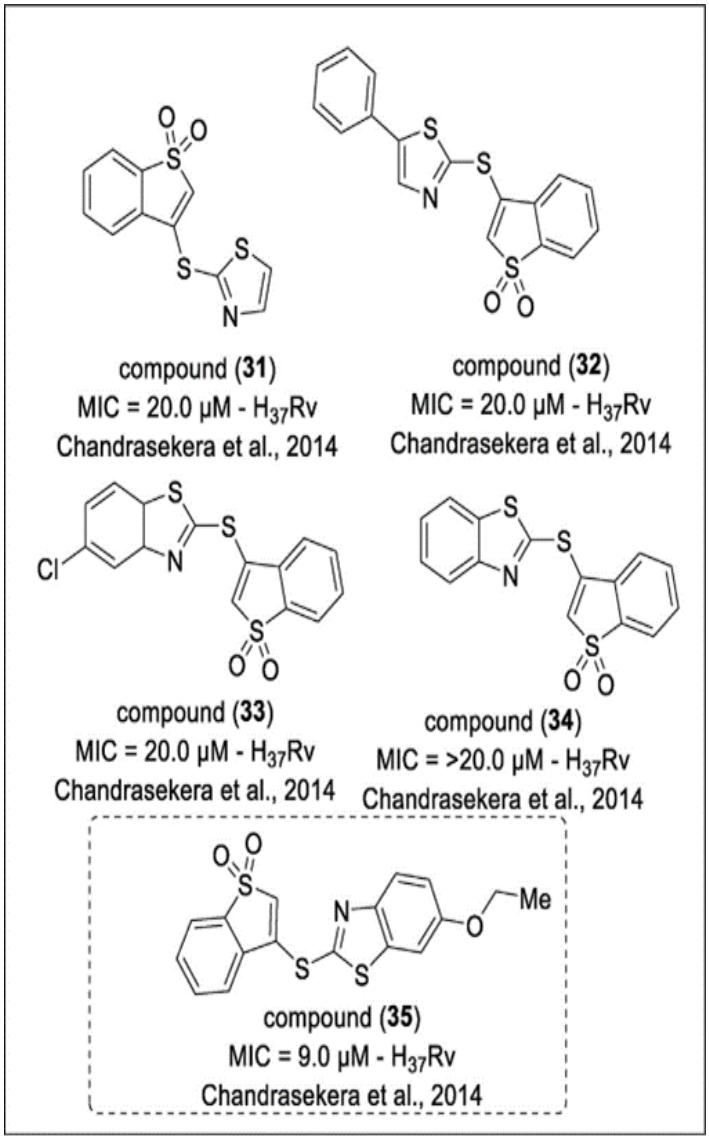


Fig. 6. By Chandrasekera et al., 2014, five new 3-substitutedbenzo[b]thiophene-1,1-dioxides (31–35) were demonstrated.

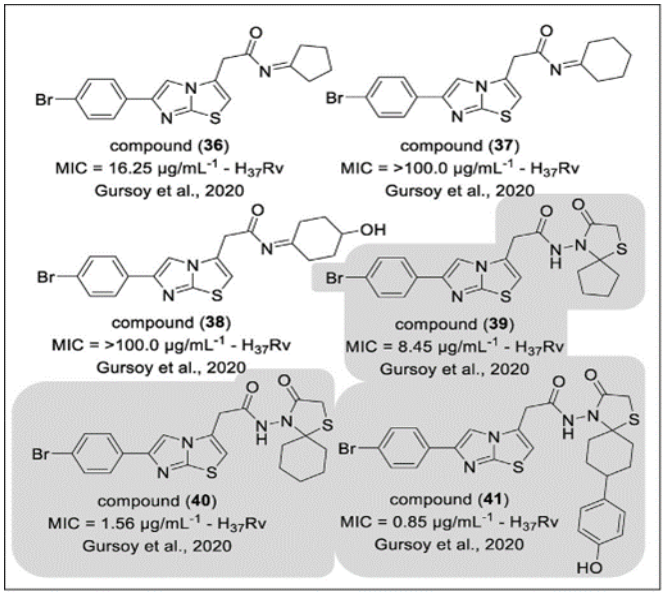


Fig. 7. According to Gürsoya et al., 2014, new acyl-hydrazone (36-38) and spirothiazolidinone (39-41) have been discovered.

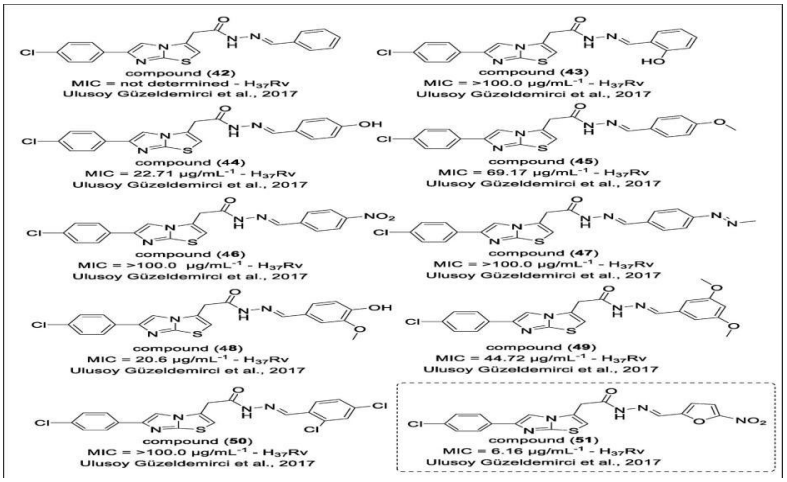


Fig. 8. Ulusoy Güzeldemirci et al., 2011 discovered ten novel arylidenehydrazide analogs with imidazole [2,1-b] thiazole (42-51) scaffold.

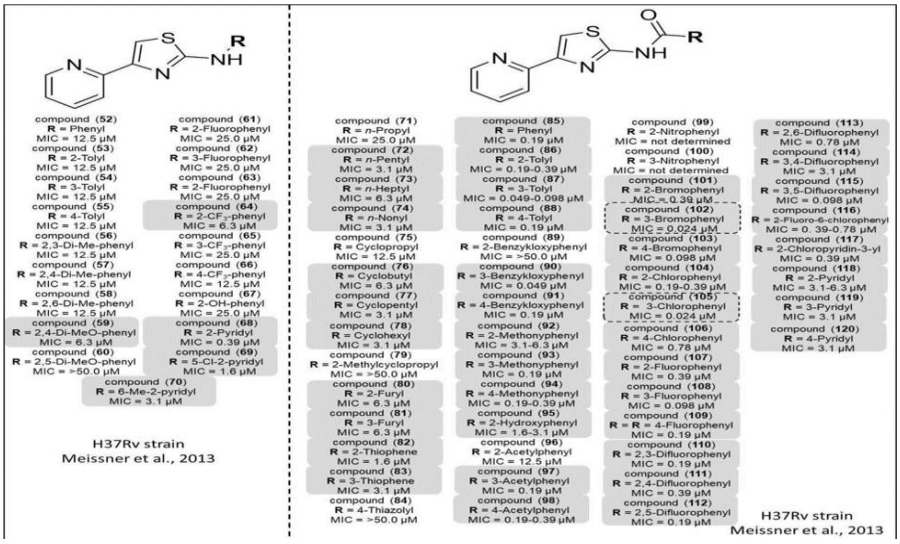


Fig. 9. Meissner et al. (2013) showed new compounds (52-120) based on 2-aminothiazoles.

Except for compounds (36-38), which showed MIC ranges of >100 g/mL1 (16.2 mM for compound 36), >100 g/mL1 (>100 mM for compound 37), and 49.2 (>100 mM for compound 38) (Fig. 7). The three most promising compounds also showed SI values of 2.8 (39), 8.9 (40), and 13.9 (41) for cytotoxicity. Therefore, against both feline coronavirus and feline herpesvirus, all drugs (36-41) demonstrated an EC50 range > 100 g/mL1.

Ten new Narylidene- (6-(4-chlorophenyl) imidazo [2,1-b]thiazol-3-yl) acetic acid hydrazide derivatives (42-51) with activity against Mtb (H37Rv-ATCC 27294) were described by Ulusoy Güzeldemirci and associates in 2011. Additionally, some substances (42-51) were regarded as anti-E. S. Aureus, anti-P. Coli, and anti-S. Anthrax. Except for compound 51, which showed a promising MIC range of 6.1 g/mL1, and compound (42), whose MIC range was not measured (Fig. 8), the compounds (43–50) had a moderate MIC range of 20.6–>100.0 g/mL1 to Mtb [98]. Additionally, all derivatives (42-51) displayed IC50 values ranging from 32 to 128 g/mL1 to E against gram-positive and gram-negative bacteria. 128 g/mL1 of E. coli to S. 64 - >128 g/mL1 of aureus P. aeruginosa.

A comprehensive series of new 2-aminothiazole derivatives (52-130) were synthesized, thoroughly described, and tested by high throughput screening (HTS) against Mtb (H37Rv-ATCC 27294) by Meissner and colleagues in 2013. All substances underwent evaluation, with MIC ranges of 0.024 to >50 M (Figs. 9 and 10). Two of these, 3-bromobenzoyl (102) and 3-chlorobenzoyl (105), were the only ones to have an exceptional MIC range of 0.024 M. However, compound (102) showed that it was swiftly broken down by hepatic microsomes (human cells).
Kesicki and colleagues (2010) discovered a series of 55 novel 2- aminothiazole analogs (131–178) with anti-TB activity (H37Rv-ATCC 27294) in another study. These compounds were evaluated by the authors, who found that their MIC ranged from 0.7 to >20 M (Figs. 11 and 12) [100]. The most promising drug (148) had a MIC value of 0.7 M and decreased cytotoxicity with SI 14 37. Despite evaluating the mechanism of action, the results were inconclusive [100].

Compounds with anti-TB action based on triazoles
Triazole rings are desirable medicinal chemistry moieties that exhibit well-researched biological proprieties. Xu

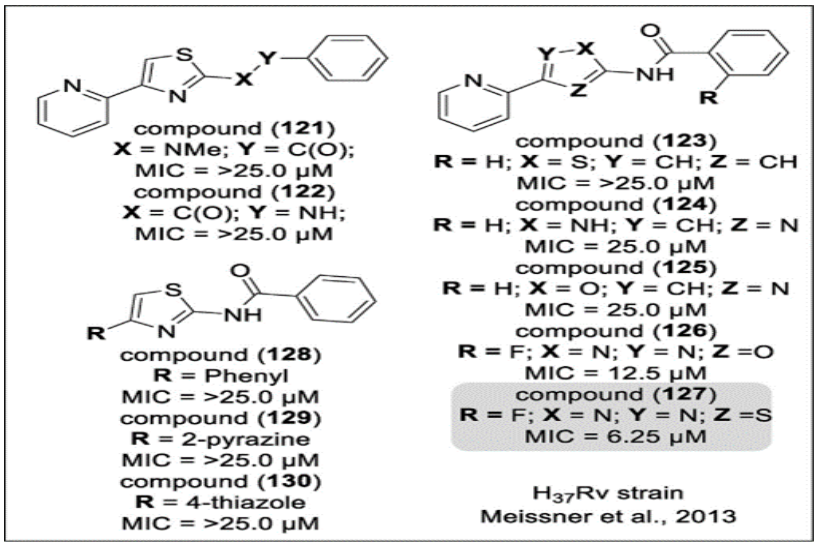


Fig. 10. Meissner et al. (2013) reported the discovery of new compounds based on 2-aminothiazoles (121–130).

A unique set of 8-OMe ciprofloxacin (CPFX)-hydrazone/azole analogs was also disclosed by coworkers (2011). Among these, three triazoles—two of which had MIC values of 4.1 M (179), 14.2 M (180), and 0.3 M (181)—and a benzothiazole derivative—presented promising anti-TB action (H37Rv-ATCC 27294). Therefore, the compounds (179-181) demonstrated an anti-bacterial (gram-positive) effect with a MIC range of >128.0 g/mL (179), >128.0 g/mL (180), and 64.0 g/mL (181) against methicillin-resistant S. epidermidis (ATCC 12228). 4.0 g/mL (179), 4.0 g/mL (180), and 0.25 g/mL (181) against methicillin-sensitive S. epidermidis (13-3). 4.0 g/ml (179), 4.0 g/ml (180), and 0.5 g/ml (181) against methicillin-resistant S. aureus (ATCC 29213). faecalis (ATCC 29212), 16.0 g/ml (179), 16.0 g/ml (180), and 1.0 g/ml (181) against Staphylococcus aureus (ATCC 33591); Staphylococcus spp. faecalis (ATCC 51299); >128.0 g/mL1 (179), >128.0 g/ml (180), and 64.0 g/ml (181) against E. coli. faecium (ATCC 700221) and E. coli at 128.0 g/ml (179), 128.0 g/ml (180), and 64.0 g/ml (181). faecium (13-7). Finally, these compounds (179-181) were tested against E and showed MIC values of 0.12 g/ml (181), 1.0 g/ml (180), and 0.5 g/ml (179) against gram-negative bacteria. E. coli (ATCC 25922, ESBLs()); >128.0 g/ml against E. 179, >128.0 g/ml against E. 180. K. pneumoniae (ATCC 700603, ESBLs()); 4.0 g/ml (179), 2.0 g/ml (180), and 0.5 g/ml (181) versus E. coli (14-11, ESBLs()); 32.0 g/ml (179), 64.0 g/ml (180), and 4.0 g/ml (181). pneumonia (7, ESBLs()),

64.0 µg/ml (179); 64.0 µg/ml (180), and 4.0 µg/ml (181) against P. aeruginosa (ATCC 27853); 16.0 µg/ml (179), 16.0 µg/ml (180), and 2.0 µg/ml (181) against Acinetobacter calcoacetious (ATCC 19606); 1.0 µg/ml (179), 1.0 µg/ml (180), and 0.25 µg/ml (181) against Enterobacter cloacae (ATCC.

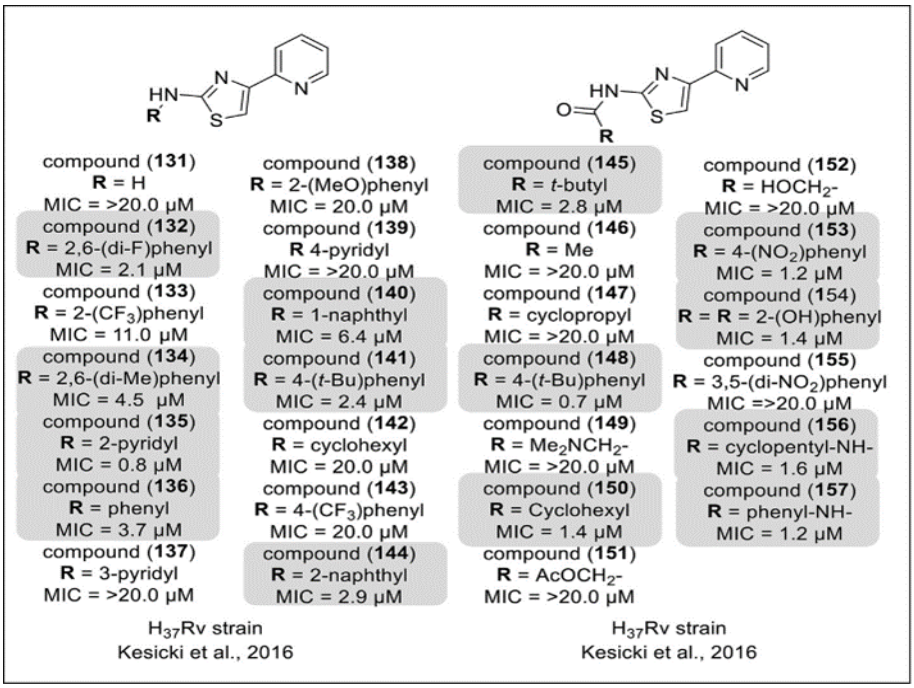


Fig 11. **New 2-aminothiazole compounds were discovered by Kesicki et al. in 2014.**

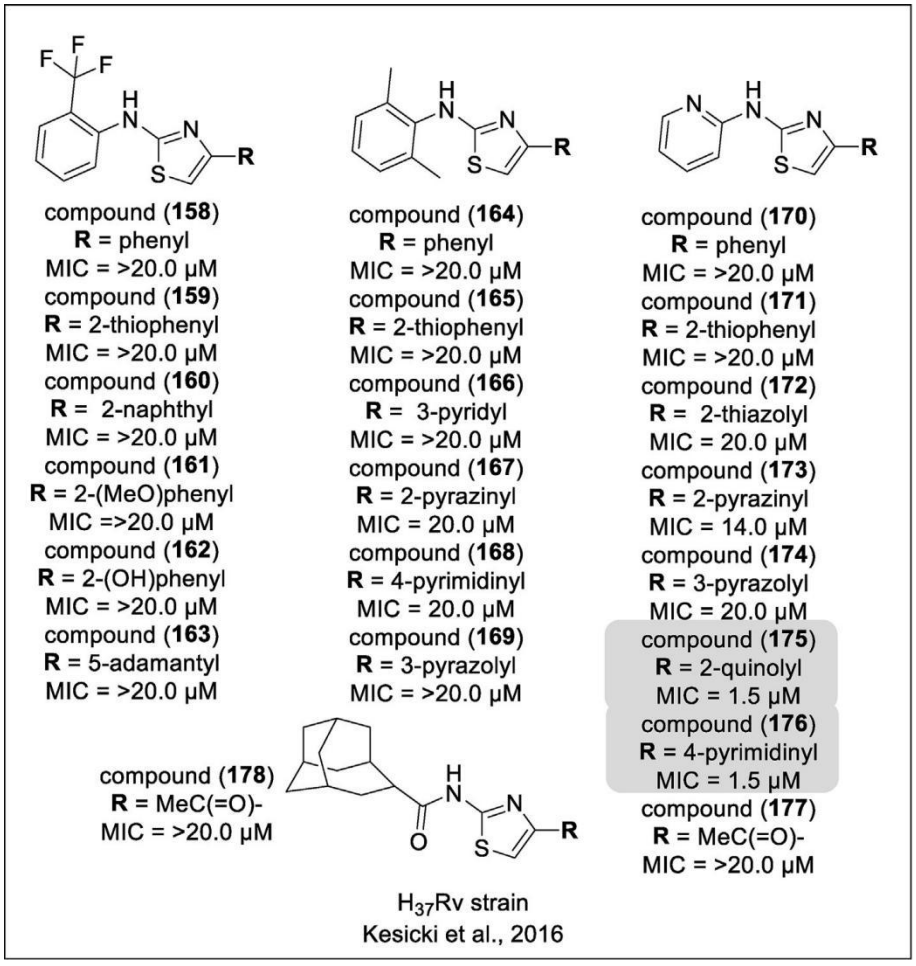


Fig. 12. Kesicki et al.'s description of new 2-aminothiazole analogs (158-178) appeared in 2014.

43560); 4.0, 2.0, and 0.5 g/ml (179, 180, and 181) against Enterobacter aerogenes (ATCC 13048); 8.0, 180, and 181) against Serratia marcescens (ATCC 21074); and 1.0, 0.5, and 0.06 g/ml (179, 180, and 181) against Morganella

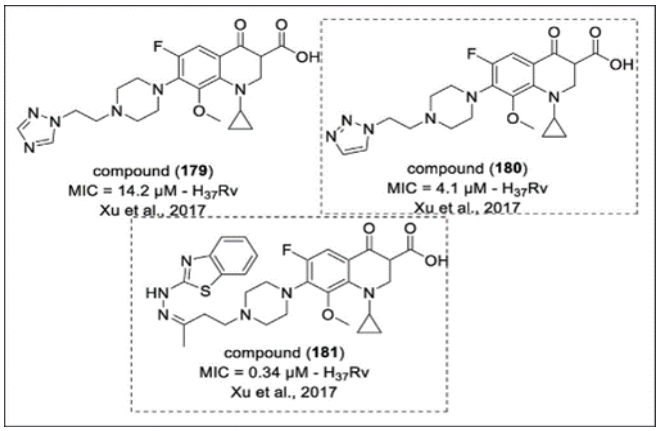


Fig. 13. Xu et al. 2011 reported the discovery of novel 8-OMe ciprofloxacin (CPFX)-hydrazone/azole compounds (179181).

morganii (ATCC 25830); 0.5 g/ml (179), 0.5 g/ml (180), and 0.06 g/ml (181) against Providentia rettgeri (ATCC 31052); 4.0 g/ml (179), 2.0 g/ml (180), and 0.12 g/ml (181) against Proteus vulgaris (ATCC 29905); 64.0 g/ml (179), Four novel 4-amino-5(4-fluoro-3- phenoxy phenyl)-4H-1,2,4-triazole-3-thiol derivatives (182185) with activity against Mtb (H37Rv-ATCC 27294) and multi-drug resistant (MDR) bacteria were described by Venugopala and coworkers in 2014. The MIC range for all substances (182-185) against the H37Rv strain was 5.5–20 g/mL1. Although derivatives (183–185) were not identified (Fig. 14), only the drug (182) displayed efficiency against MDR bacteria, showing a MIC value of 11 g/mL1. The triazole-based derivative (82) showed a solid ability to inhibit KasA enzymes by molecular modeling. Additionally, this substance (82) acted to manufacture fatty acids, which are in charge of cell membrane structure. A series of 1-(4-((2-(4- substituted phenyl) hydrazone)methyl)phenyl)-1H-1,2,4-triazole analogs (186-193) with anti-TB action (H37Rv-ATCC 27294) were synthesized, described, and evaluated by Ozadali-Sari and collaborators in 2013. The MIC range for these compounds (186-193) against Mtb was between 73.3 and 190.1 M (Fig. 15).

Five novel 3-nitroimidazole sulfonamide compounds (194–198) were reported by Papadopoulou and colleagues (2014). Additionally, this triazole

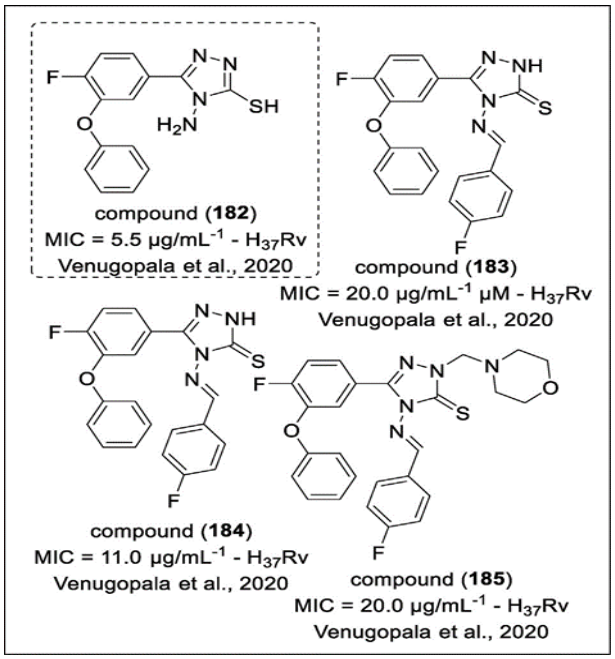


Fig. 14. Venugopala et al., 2014 demonstrated new 4-amino-5-(4-fluoro-3-phenoxyphenyl)-4h-1,2,4-triazole-3-thiolbased compounds (82-85).

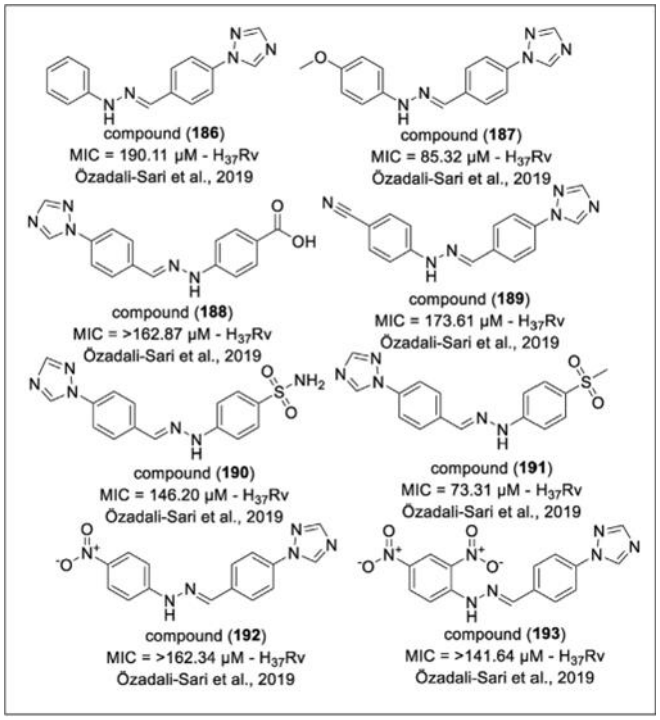


Fig. 15. Evidence of triazole conjugates in hydrazone analogs was shown by Ozadali-Sari et al. in 2013.

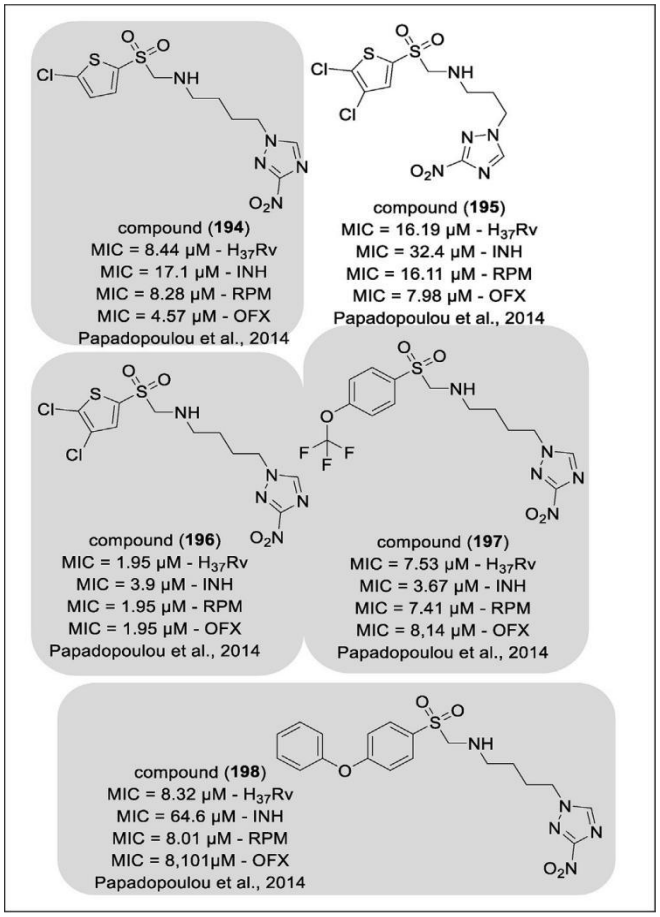


Fig. 16. By Papadopoulou et al., 2014, novel 3-nitrotriazole sulfonamide derivatives (194–198) were described.

The most promising molecule (196) had a MIC value of 1.95 M, whereas other derivatives (194-195, 197-198) displayed MIC values ranging from 7.53 to 16.19 M (Fig. 16). Analogs (194-198) were evaluated for Mtb inhibition (H37Rv-ATCC 27294). Furthermore, their percentage of inhibition against the H37Rv strain ranged from

81% to 100% [104]. Additionally, these drugs (194-198) were tested against three separate strains of resistant M. tuberculosis, showing MIC (% inhibition) values of 3.6 to 64.6 M (62-85%), 1.95-16.11 M (93-100%), and 1.95-8.14 M (82-98%) (Fig. 16). Seven novel triazole-based diindolylmethane analogs (199-205) with anti-TB action (H37Ra) were demonstrated by Danne and colleagues in 2013. While compounds (200) and (205) demonstrated IC50 values of 14.8 and 6.2 g/mL1, respectively (Fig. 17), against active forms of Mtb, and an IC50 range between 0.12 and 2.96 g/mL1, against dormant forms of Mtb, the compounds (199, 201–204) revealed promising IC50 values from 0.22-2.27 g/mL1. The ability of these derivatives (199-205) to block the DprE1 enzyme was also demonstrated by molecular modeling.

The anti-TB activity of 22 new triazole-5-thione derivatives (206-227) was synthesized, described, and evaluated by Vora et al. (2013) (H37Rv-ATCC 27294). MIC values for the compounds (206, 209-211, 2010-2014, and 220-227) were between 12.5 and >100 M.

MIC values for the compounds (208, 213, 215, and 219) ranged from 3-1-6.25 M (Fig. 18). Triazole derivatives revealed excellent MIC values of 0.19 M (207), 0.39 M (212), and 0.39 M (214) (Figs. 18 and 19). Additionally, using a fluorescence-based test, the most effective compounds (207, 212, 214) were able to inhibit the enoyl acyl carrier protein reductase (InhA), with IC50-InhA values of 0.09 M (207), 0.19 M (212), and 0.12 M (214). Using 14 1,2,4-triazole analogs (228-241) as anti-infective drugs, Karczmarzyk and colleagues (2014) reported in vitro testing against Mtb (H37Ra), Mycobacterium phlei (M. phlei), Mycobacterium smegmatis (M. smegmatis), and Mycobacterium limerick (M. limerick). Except for compounds (233-234, 237) that were inert, the investigated compounds (228-232, 235-236, 238-241, at 250 g) demonstrated an inhibition zone from 10.6 to 26.9 mm against Mtb. As a result, it was feasible to see that compound (231), the most potent triazole derivative, had a MIC value of 0.97 g/ml, while compounds (228, 235, 238, and 241) displayed a MIC range of 62.5 g/ml (Fig. 19). The outcomes showed that the MIC values of these compounds (228, 235, 238, 241) against M ranged from 31.2 to 500 g/ml. Chemical (231) showed a MIC value of 7.81 g/ml, compared to Phlei, who reported Phlei. Additionally, the MIC ranges for these five compounds (228, 231, 235, 238, 241) against M were between 62.5 and >500 g/ml. as well as M. correspondingly, limerick. All substances (228-241) were shown to be able to act on and link to the P450 CYP121 enzyme target by molecular modeling.

As antiTB drugs (H37Rv-ATCC 27294), Garg and colleagues (2014) developed and analyzed 21 novel amino acid 1,4-disubstituted-based triazole analogs (242-262). The MIC values for the compounds (242-247, 249, 251-258, and 261-262) were 25.5 g/ml, while the MIC ranges for compounds (248, 250), and (259-260), were 3.25 g/ml and 6.25 g/ml, respectively (Fig. 20). The four most promising compounds (248, 250, 259-260) also demonstrated non-cytotoxicity against mouse macrophages with CC50 values > 100.0 g/ml and SI values from 16-32. According to the molecular analysis, the DprE1 target protein (Mtb) might bind to these analogs [108]. 20 novel [1,2,3]-triazole compounds were disclosed in a series by Nalla and collaborators (2012) (263-282). The five most promising compounds had MIC/SI values of 3.12 g/ml/6.4 (268), 6.25 g/ml/4.5 (269), 3.12 g/ml/6.0 (270), and 6.25 g/ml/5.8 (275), respectively, when tested against Mtb (H37Rv-ATCC 27294) and their cytotoxicity at 50 g/ml (RAW264.7 cells). 17. g/ml/5.9 (277) and 1.5 g/ml/16.4 (281) of the triazole-diindolylmethane analogs (199-205) described by Danne (Fig. 21). The et al., 2013 [105], as well. MIC data for further compounds (263-267, 271-274, 276–278, and 282)

(Fig. 21) vary between 12.5 and 50.0 g/ml.

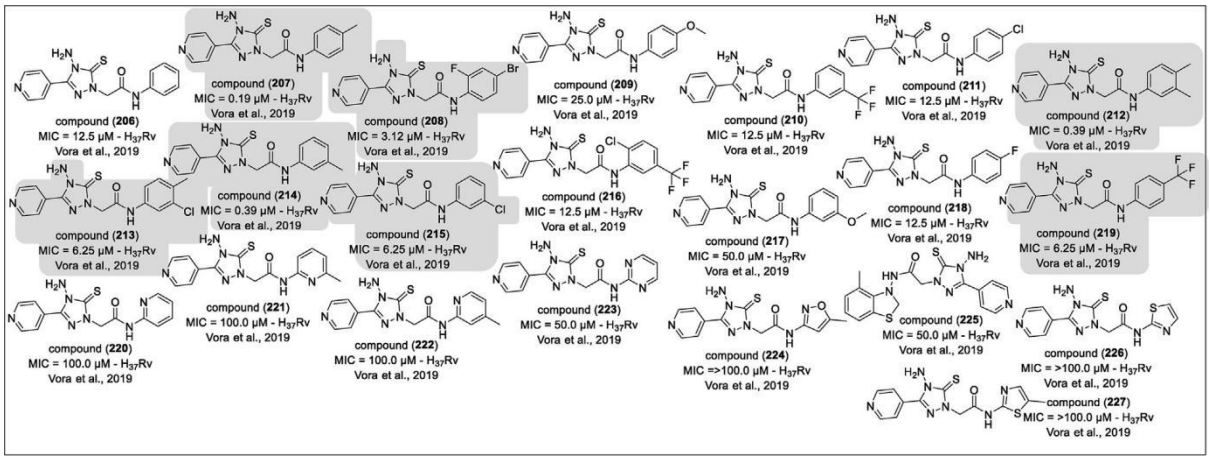


Fig. 18. A-B. Analogues of triazole-5-thione (206-227) were reported by Vora et al. in 2013.

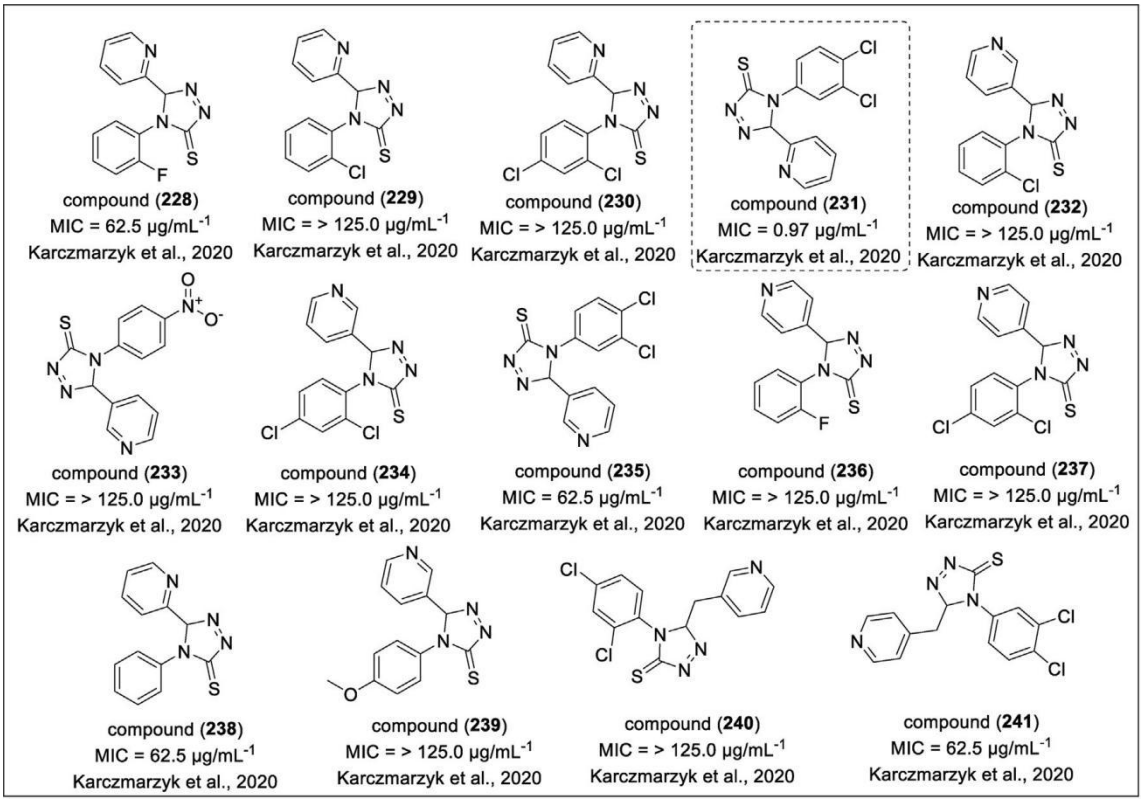


Fig. 19. Karczmarzyk et al., 2014 presented novel triazole-based analogs (228-241).

Sixty new triazolopyrimidine derivatives (283-342) were synthesized, described, and tested for anti-Mtb activity by Zuniga and colleagues in 2011 (H37Rv-ATCC 27294). Therefore, these substances were tested for their ability to kill Mtb and their cytotoxicity in HepG2 cells. The most effective triazolopyrimidine-based analogs showed MIC/SI ranges of 3.1 M/>32 (283), 4.4 M/4.5 (290), 3.0 M/>30 (291), 0.8 M/>130 (293), 5.8 M/>17 (299), 2.9 M/>34 (300), In conclusion, the MIC values for the other compounds (284-289, 292, 294-298, 302-311, 313-314, 316-319, 322, 228-230, 337-340, 342) ranged from >20 M (Figs. 22 and 23).

Goud et al. (2011) created 24 novel 1,2,3-triazolyl xanthenone analogs (343–366) and investigated how they affected Mtb (H37Rv–ATCC 27294) in a biological sense. The compounds (343–344, 346–354, 356–360, 362, 364–365) exhibited MIC values from 12.5 to >25 μg/mL1, while the most potent compounds presented MIC/SI ranges of 3.1 μg/mL 1/18.1 (345), 6.25 μg/mL1/21.1 (355), 3.1 μg/mL1/18.1 (361), and 6.25 μg/mL1/22.1 (363) (once that only the most potent compounds demonstrated cytotoxicity assay at 50 μg/mL1 using HEK cell line) (Fig. 24). The MIC values for these substances (343–366) against gram-positive and gram-harmful bacteria ranged from 3.1 to >100.0 g/mL1 to S. 3.1->100.0 g/mL to Bacillus cereus, 3.1->100.0 g/mL to Escherichia coli, 3.1->100.0 g/mL to Pseudomonas aeruginosa, and 3.1->100.0 g/mL to Enterobacter aerogenes. All triazole-based derivatives (343–366) demonstrated antifungal activity, with IC50 values ranging from 3.1–100.0 g/mL1 for both Aspergillus niger and Candida albicans. In another study, Ashok et al. (2012) synthesized 15 novel 1,2,3-triazole-based spirochromene derivatives (367–381) and evaluated their anti-TB activities (H37Rv-ATCC 27294). All of the compounds (367–381) were described, but only compound (367) revealed its X-ray crystal structure. Thus, the compounds (368–369, 371–374, 376, 378, 380–381) showed MIC range from 6.5 to >25 g/mL1 (15.9-75.8 M) against Mtb, while the compounds showed excellent MIC/SI values of 1.5 g/mL1(4.7 M)/20.1 (367), 1.5 g/mL1(4.3 M)/22.0 (370), 1.5 g/m.

In order to combat drug-sensitive and multidrug-resistant Mtb, Yan and collaborators (2012) reported a series comprising 12 novel isatin propylene-containing triazole-based methylene-moxifloxacin derivatives. Thus, against H37Rv (ATCC 27294) and MDR-TB strains, respectively, all compounds (382-393) showed good anti-effects with MIC ranges of 0.05 to 1.56 g/mL-1 and 0.06-1.0 g/mL-1 (Fig. 26). With CC50 and SI ranges between 2.6 and 160.0 to the H37Rv strain, these substances (382-393) showed cytotoxicity against VERO cell lines (Fig. 26). A series of 21 brand-new 4-alkoxy-triazoloquinolone analogs (394–414) were presented by Carta and colleagues in 2013 with effects against Mtb (H37Rv-ATCC 27294) and cytotoxicity against VERO cells. The compounds (394–398; 400–409; 411-414) demonstrated MIC values against Mtb (H37Rv) ranging from 25.3–100.0 M, whereas the most potent compounds (399) had MIC/SI ranges of 6.9 M/13.1.

6.6 μM/14.2 (410) (Fig. 27). The chemical (399) was also.

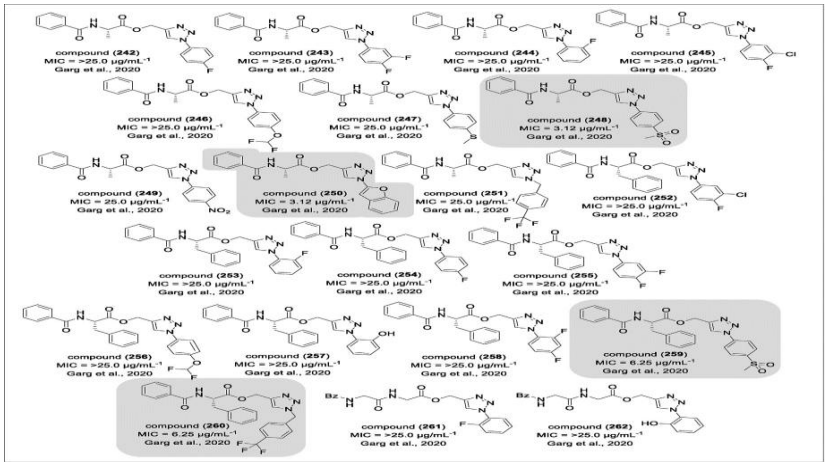


Fig. 20. A-B. Garg et al.'s 2014 description of amino acid-linked 1,4-disubstituted-based triazole analogs (242-262).

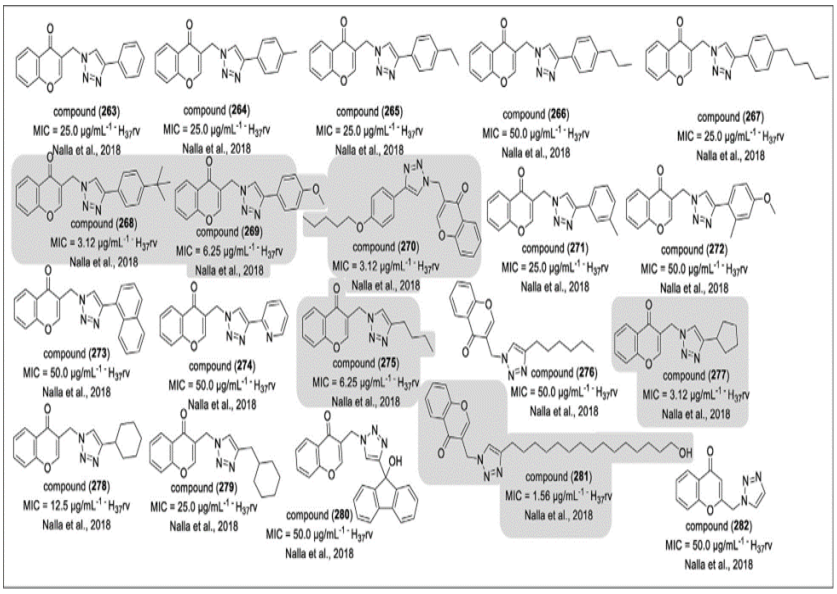


Fig. 21. By Nalla et al., 2012, new triazole-based compounds (263-282) were developed.

MIC values ranging from 4 to 32 M were found when tested against 11 additional M. tuberculosis clinical isolate strains (MDR, multidrug-resistant strains).

Twenty-one new bis-substituted cyclam-based compounds (415–435) with anti-TB activities (H37Rv–ATCC 27294) were synthesized and described by Spain et al. (2012). The other derivatives (415-431, 433, 435) showed better MIC values between 3.13 and 6.15 M, whereas two compounds (432, 434) presented MIC ranges of 50 M (432) and 100 M against Mtb (Fig. 28). The drug (435) was also tested utilizing the Zebrafish model against tdTomato-fluorescent Mycobacterium marinum. The chemical (435) was thus found to have the ability to reduce Mycobacterium marinum infection, as evidenced by the experimental results (in vivo, by fluorometry assay: fluorescence/embryos 2000). Yu and colleagues (2010) reported the synthesis and evaluation of 1,8-disubstituted-based cyclam analogs (436-437) in a different study. These substances (436-437) impacted clinical isolate strains of Mtb and Mtb H37Rv. Only the compounds (436-437) with MIC values of 6.25 M (H37Rv strain) demonstrated decisive anti-Mtb actions. The MIC values for both compounds (436-437) against all virulent and drug-resistant strains were 6.25 M (IZN-1, isoniazid-resistant strain), 3.13 M (RIF-1, rifampicin-resistant strain), and 6.25 M (ETH-1, ethambutol-resistant strain) (Fig. 29).

3. Anti-TB thio- and semicarbazone-based chemicals activity

In several therapeutic disciplines, thio- and semicarbazone are essential and advantageous constituents. Nine novel pyrazinyl-containing ferrocenyl analogs (438446) with biological actions against Mtb (H37Rv-ATCC 27294) were

discovered by Stringer and coworkers in 2011. While the other derivatives (439-443) showed MIC ranges from 10 to 125 g/mL1, the compounds (438, 444-446) displayed outstanding MIC values of 0.39 g/mL1 (438), 0.41 g/mL1 (444), 0.96 g/mL1 (455), and 0.51 g/mL1 (446) (Fig. 30). Additionally, the antimalarial potency of each molecule was tested against Plasmodium falciparum, with compounds (139) and (145) showing the most robust results with IC50 values of 1.58 M and 2.99 M, respectively. In contrast, other analogs (438, 140-444, 146) showed IC50 values ranging from 3.77>100 M. Additionally, only the compounds (445-446) against Trichomonas vaginalis were assessed and found to have IC50 values of 10.41 and 14.27 M, respectively. As a result, compounds (438, 441-446) lacked action against mammalian normal cells at 100 g/ml, whereas compounds (439-440) displayed CC50 values of 20 M.

Three new Ag(I)-based compounds with thiosemicarbazone as ligands (447-449) and an anti-TB action (H37Rv-ATCC 27294) were reported by Silva and coworkers in 2014. For complexes (447-449) against Mtb, all substances established potential MIC ranges between 2.29 and 2.56 g/ml (3.75-4.05 mol/L1) and SI values between 4.68 and 20.06 (Fig. 31). In addition, the antiproliferative activity of these complexes (447-449) was evaluated in two different breast cancer cell lines, with IC50 values of 13.19 M (447), 20.90 M (448), and 11.07 M (449) against MCF-7 tumor cells and 9.54 M (447), 9.53 M (448), and 3.87 M (449) against MDA-MB-231 tumor cells, respectively. Additionally, the compounds (447-449) showed a promising IC50 value of 1.49 M (447), 2.64 M (448), and 2.27 M (449) against lung tumor lines (A549 cells), which demonstrated an antiproliferative action. The compounds (447-449) had high CC50 values from 2.2 to 5.1 M when the cytotoxicity was evaluated using MCF-10A standard cell lines. Six novel metal-based Mn(II) compounds with thiosemicarbazone derivative as ligands (450–455) were synthesized, described, and evaluated as a biological treatment for TB (H37Rv-ATCC 27294) by Oliveira and coworkers in 2014. All compounds underwent crystallographic studies as well. These substances' cytotoxicity (450–455) was assessed using VERO cell lines. As a result, all drugs (450–455) displayed positive MIC/SI ranges between 0.78 and 23.8 g/ml/SI 14 1.6–80.1, or 1.31–50.69 M (Fig. 31).

A series of 11 novels of quinolone-based thiosemicarbazone derivatives (456-466) with anti-TB (H37Rv-ATCC27294) and anti-Plasmodium (Pf 3D7) actions was disclosed by Beteck and colleagues (2013) [120]. While compounds (442, 444, and 445) showed an anti-Mtb action and displayed MIC ranges of 2.7 M (442), 2.0 M (444), and 4.8 M (445) (Fig. 32), compounds (440, 442-447) displayed MIC values from 10.2 to >125.0 M. The MIC ranges for all drugs (440-450) against Mtb were 2.0 to >125 g/mL (M). Additionally,

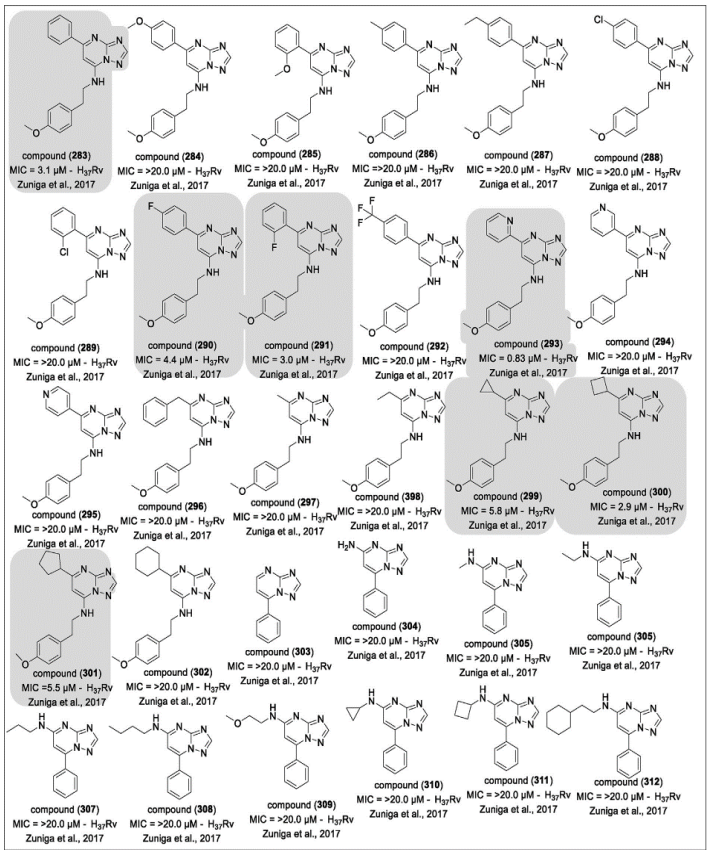


Fig. 22. A-B. Zuniga et al., 2011 described novel triazolopyrimidine-based analogs (283–312).

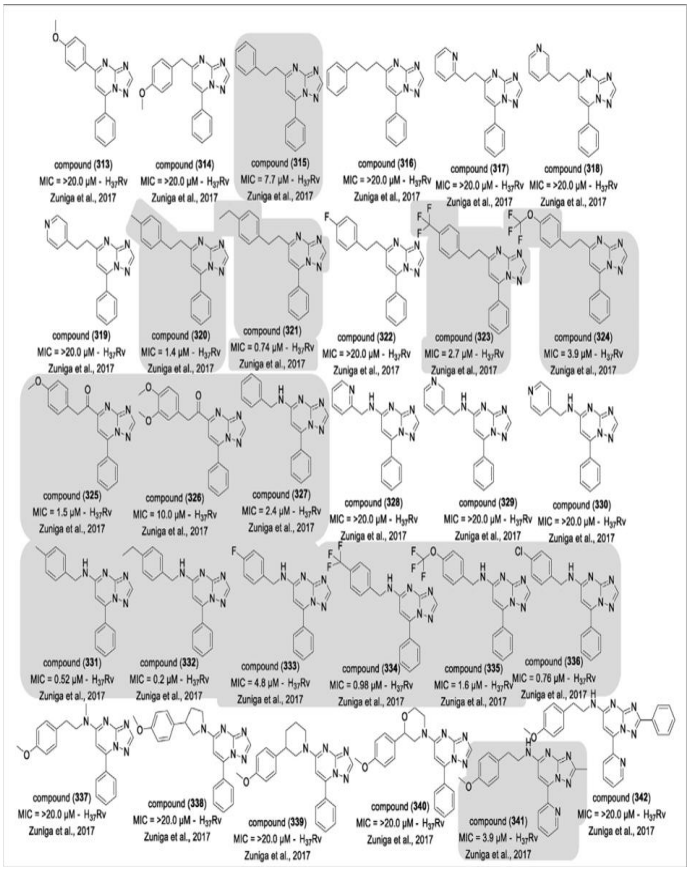


Fig. 23. A-B. Zuniga et al. 2011 presented new compounds (313-342) based on triazolopyrimidine.

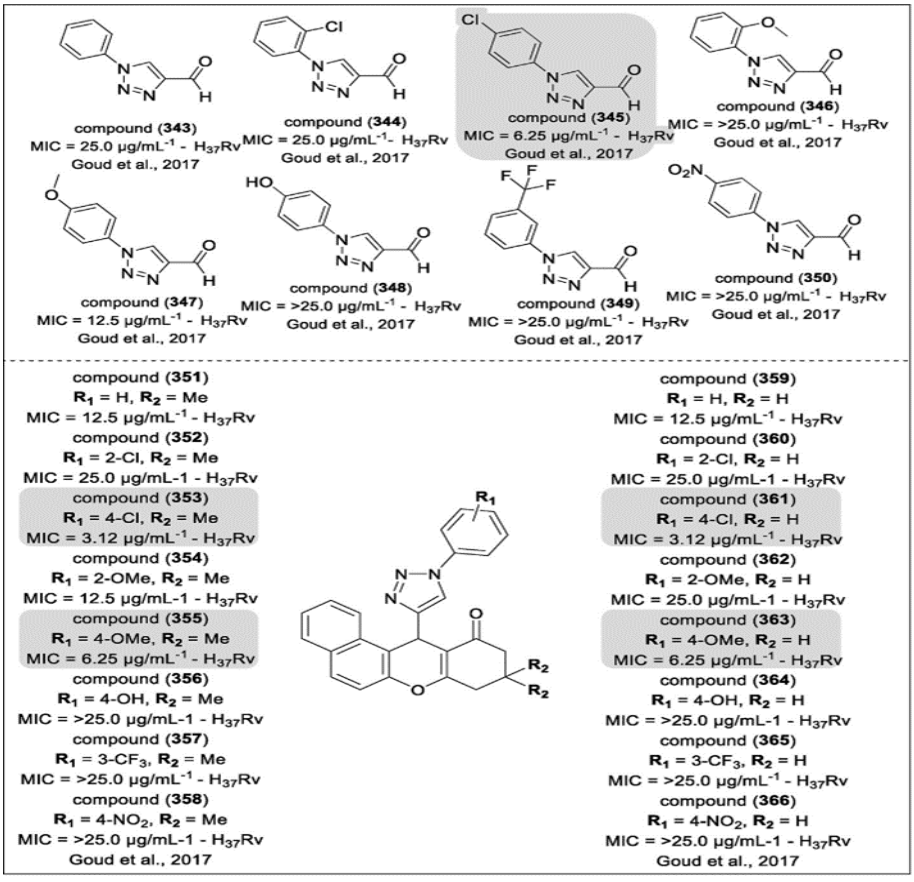


Fig. 24. By Goud et al., 2011, new triazolyl xanthene-based compounds (343–366) were displayed.

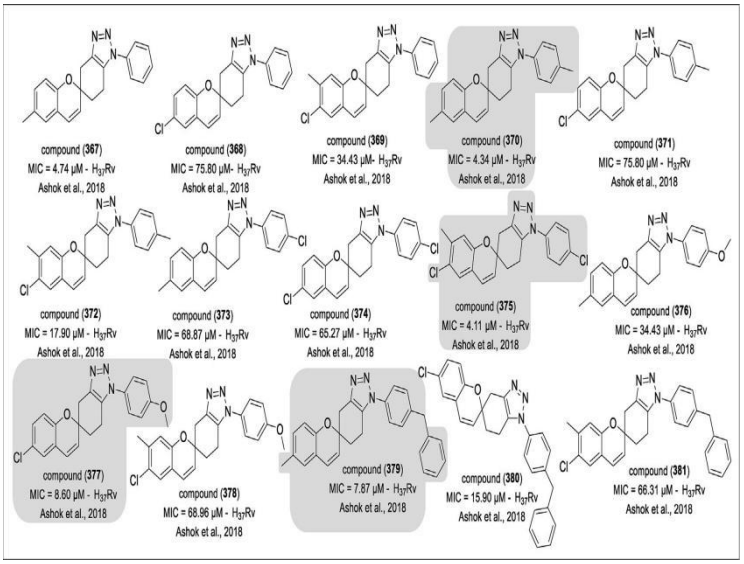


Fig. 25. By Ashok et al., 2012, novel triazole-based spirochromene analogs (367-381) were developed.

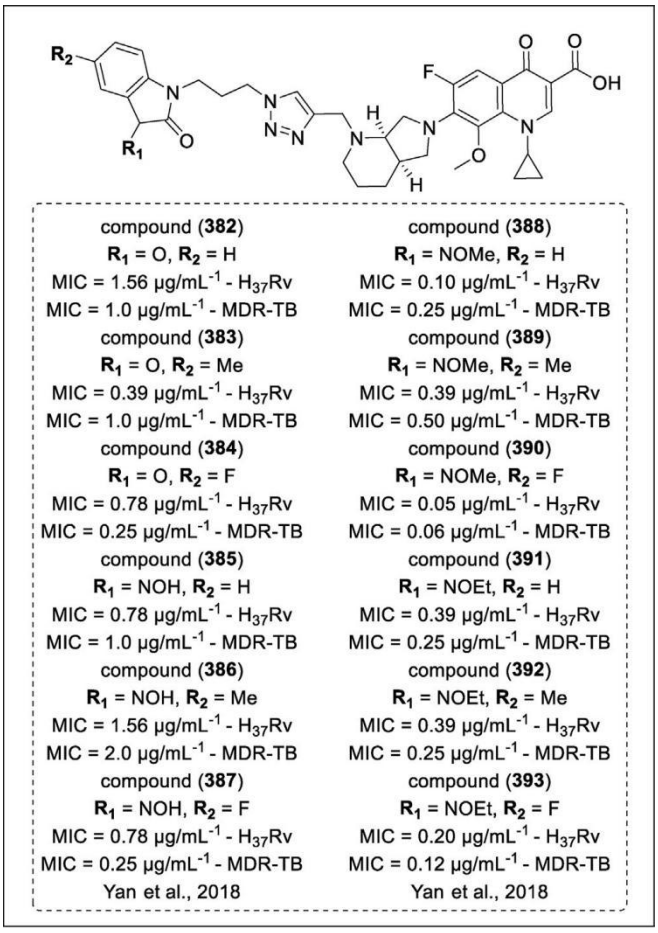


Fig. 26. Yan et al. (2012) developed novel triazole-4-methylene-moxifloxacin analogs (382–393) containing isatin-propylene.

Against Plasmodium falciparum, these analogs (440, 442-447) displayed IC50 values of 1.2-24.6 M, except compounds (441, 448-450) that lacked a determined IC50 value. A thiosemicarbazone derivative (467) was evaluated against two Mtb strains, lepB-UE (SPAM13C) and wild-type (H37Rv), in a different study by Bonnett et colleagues (2010) [121]. The MIC values for this drug (467) against the Mtb strains SPAM13C and H37Rv, respectively, were 9.0 M and 18.0 M (Fig. 32). Moreover, the chemical (467) was tested for cytotoxicity. exhibited SI values of 1.2 (SPAM13C) and 0.6 (H37Rv) and CC50 values of 11.0 M.

4. Final thoughts and outlook

Interesting moieties in medicinal chemistry include thiazole, triazole, thiosemicarbazone, and semicarbazones for creating novel drugs against infectious disorders, particularly Mtb. Here, dozens of compounds were highlighted and showed anti-tb solid action. Here, the online program pkCSM was used to assess the physicochemical characteristics of thiazole, triazole, thiosemicarbazone, and semicarbazone analogs (Table S1, Supplementary Material). This revealed that most of the compounds displayed tolerable physicochemical parameters per Lipinski's rule (Table S1, Supplementary Material). Furthermore, the analysis between MIC values and cLogP (Fig. 33) showed that the majority of the most active compounds (MIC 10.0 M) described in this work are by the Lipinski rules (cLogP 5) (89.6% of the molecules in Fig. 33). In vitro tests were performed against the H37Rv strain and several Mtb lines, including resistance Mtb strains, for the majority of the data included in this review. The strongest thiazole (1, 5-11, 13-14, 29-30, 35, 39-41, 51, 59, 64, 68–70, 72–74, 80–88, 90–95, 97–98, 101–120, 127–132, 134–136, 140–141, 153–154, 156–157, 175–176), triazole (180–182, 194, 196–199, 201-206, 207–208, 212-215,

The following analogs are emphasized in their respective figures according to their potency (10 M and ten g-ml): thio- and semicarbazone-based (438, 444-449, 452-454, 458, 460-461, 464). However, only a small number of variants evaluated cytotoxicity assays and in vivo tests with the

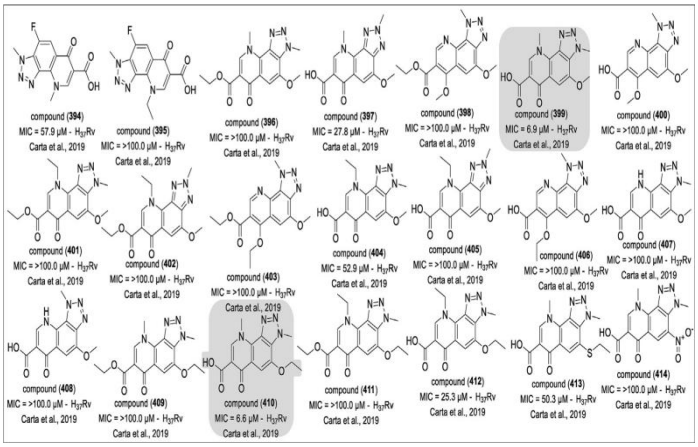


Fig. 27. By Carta et al. in 2012, new alkoxy-based triazoloquinolone analogs (394–414) were reported.

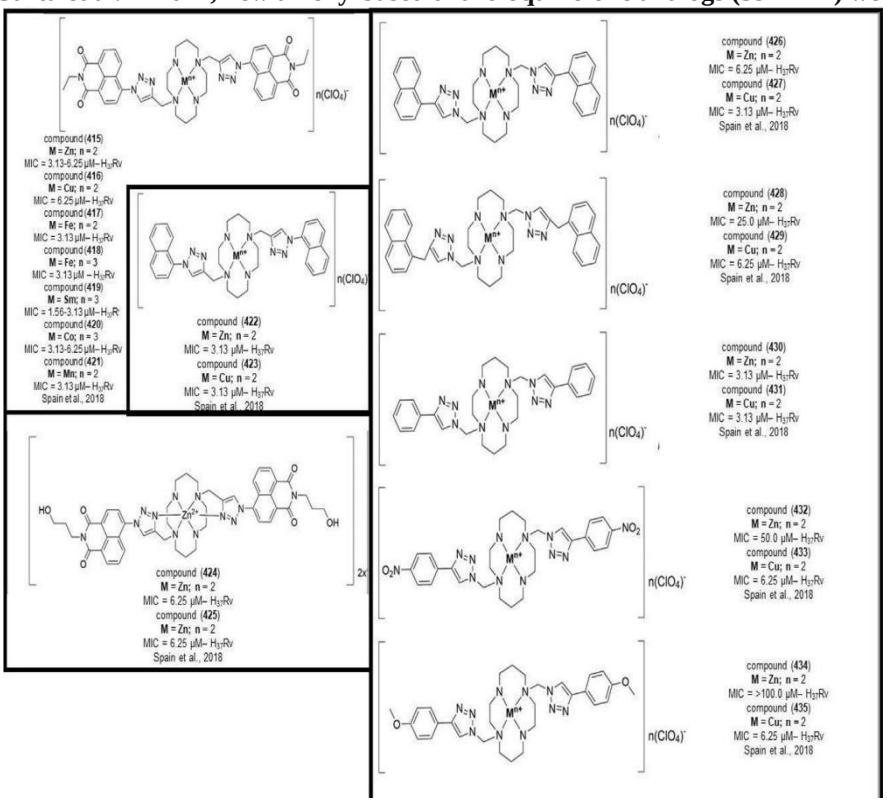


Fig. 28. Spain et al.'s 2012 publication on novel bis-substituted-based cyclam derivatives (415–435).

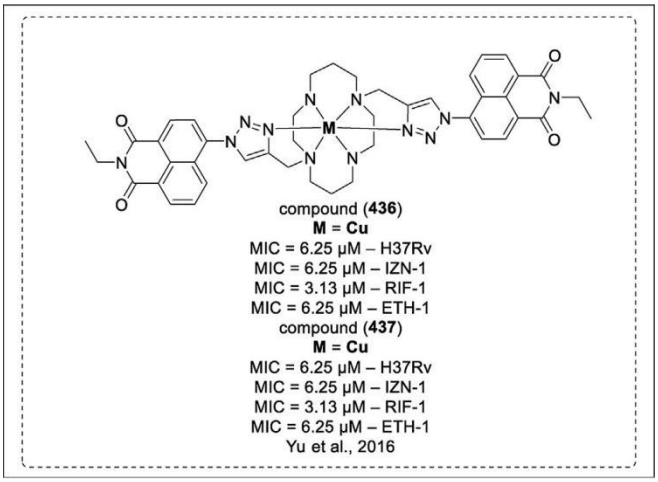


Fig. 29. Yu et al., 2010 displayed new 1,8-disubstituted-based cyclam analogs (436-437).

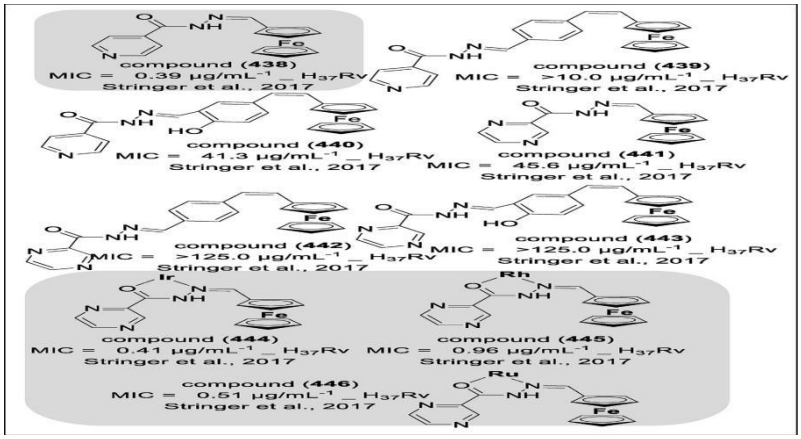


Fig. 30. Stringer et al. (2011) found new isonicotinyl/pyrazinyl-based ferrocenyl compounds (438–446).

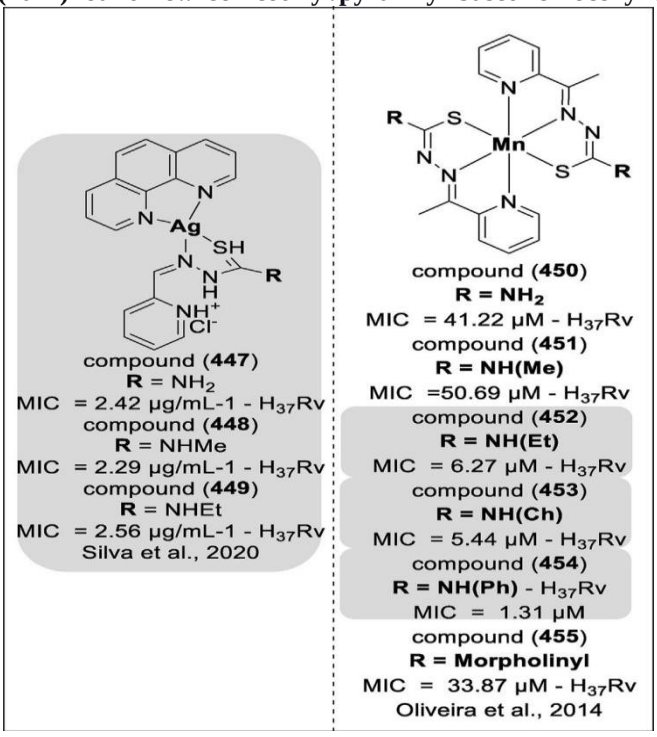


Fig. 31. Six fresh Mn(II)-conjugates having thiosemicarbazone as ligands were demonstrated by Oliveira et al. in 2014, while three new Ag(I)-conjugates containing thiosemicarbazone as analogs (447–449) were reported by Silva et al. in 2014.

The goal is to verify that substances with IC50 values greater than 10 M have an anti-TB effect. Even fewer people are involved in the quest to discover the mechanism of action. Therefore, the outcome could have been more conclusive despite evaluating the mechanism of action in several compounds. Therefore, molecular changes can enhance bioactivity, cytotoxicity, pharmacodynamics, and pharmacokinetic characteristics. In light of this, we emphasize the recent developments in the design of drugs for treating tuberculosis that involve these pharmacophore groups, such as thiazole, triazole, and thio and semicarbazone conjugates.

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