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Review Article

1,2,4-Triazolo[1,5-a]pyrimidines as significant scaffold in drug discovery

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ABSTRACT

Over the years, 1,2,4-Triazolo[1,5-a]pyrimidine (TP) emerged as an important scaffold in medicinal chemistry due to its vast application in designing novel anti-cancer, antimicrobial, antiviral, antiparasitic, and CNS-modulating agents. Recently, publications of TP analogues with diverse biological activities have increased markedly. In this review, we focus on the most important applications of TP scaffold in medicinal chemistry

1. *Introduction*

The triazolopyrimidine derivatives are hetero-bicyclic organic compounds that gained considerable attention recently owing to their vast pharmacological activities. Four possible isomers of 1,2,4-triazole-fused pyrimidines may exist (**Fig.1**).[1–4] Among them, 1,2,4-triazolo[1,5-*a*] pyrimidine (TP) has gained the most attention due to its variety of applications in agriculture and medicinal chemistry. Some natural TPs have been identified such as essramycin **1**(antibacterial drug) isolated from the broth of.

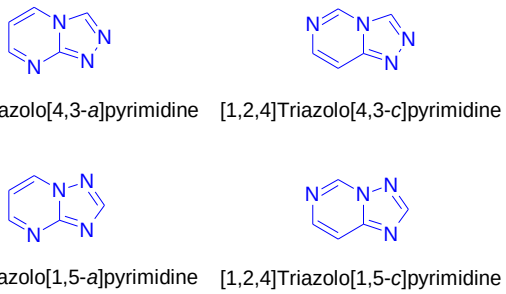


Fig. 1. Four representative isomers of 1,2,4-triazolopyrimidines

the marine species *Streptomyces*[5], in addition to some volatile oils **2-5** (**Fig.2**) isolated from *Polygonatum odoratum, Poncirus trifoliata*, *Paris polyphylla*, *Anchusa azurea*, respectively However, the majority of 1,2,4-triazolo[1,5-*a*] pyrimidine derivatives were synthesized compounds. Interestingly, the first synthetic 1,2,4-trizaolo[1,5-*a*] pyrimidine (TP) scaffold was reported by *Bulow & Hass* in 1909. [6]

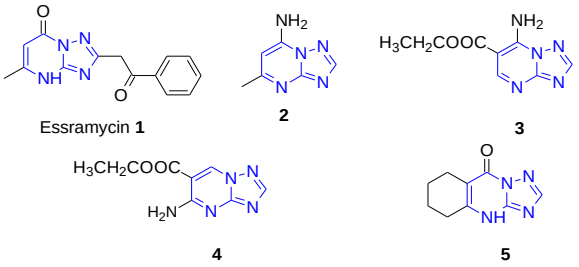


Fig. 2. Structures of TP derivatives **1-5.**

2. Biological activities of 1,2,4-triazolo[1,5-*a*]pyrimidine derivatives

2.1. Anti-cancer activity

Cancer is the second leading cause of death in the world according to the World Health Organization (WHO), and till now, there is no complete cure effective against disseminated cancer. The TP scaffold has emerged as a prominent scaffold in developing promising target-based anti-cancer agents in the past few decades. These oncotargets include six categories: DNA damage repair system, signal transduction pathway, ubiquitin-proteasome pathway (UPP), epigenetic modification, tumor microenvironment (TME), and multidrug resistance (MDR).

2.1.1. DNA damage repair system target

DNA damage response (DDR) is a sophisticated process that cells develop to repair different DNA damage and preserve genome structure.[7,8] Although most damages undergo DNA repair, such repair isn't 100% efficient, and the accumulation of driver DNA mutations plays an important role in cancer cell growth.[9] Hence, targeting DDR became a promising approach to developing anti-cancer agents.[10]

2.1.1.1. Tubulin inhibitors

Heterodimers of globular tubulins are the main building blocks of the cylindrical skeleton of microtubules essential for many vital cellular functions[11]. Mutations and overexpression of tubulins leading to mitotic spindle formation and mitotic division, which disrupts this process, therefore tubulin inhibition is a major approach in developing chemotherapeutic agents [12–14].

A study made by *Zhang et al.*[15] led to the development of cevipabulin (TTI-237) **6** as a potent microtubular inhibitor that can inhibit the growth of several cancer cell lines. TTI-237 (Fig.3) acts by competing with a vinblastine binding site, not paclitaxel. However, TTI-237 inhibited depolymerization of microtubules like paclitaxel, proving that TTI-237 displayed mixed properties between vinblastine and paclitaxel. Unfortunately, the phase I clinical trial of TTI-237 was ended due to its toxicity.[16]

Additionally, in 2019, *Yang et al.*[17] reported a series of TP derivatives as restricted combretastatin-4 (CA-4) analogs showing marked anti-tubulin activity. Among them, compound **7** (Fig.3.) showed the most promising antitumor activity against the three tested cell lines, A549, HeLa, and HCT116, with IC_{50} values of 1.02 μM, 0.75 μM, and 10.91μM, respectively, compared to CA-4 with IC_{50} values of 0.013 μM, 0.21 μM, and 6.10 μM, respectively. Moreover, compound **8** (Fig.3.) showed the highest tubulin inhibiting activity (IC_{50} = 9.9 μM) compared to CA-4 (IC_{50} = 4.22 μM). Furthermore, molecular modeling showed that the colchicine binding site was occupied by the TP derivative. Further structural modification of compound **7** by removing acetyl- and methyl- groups to obtain a series of TP analogs, among them compound **9** (**Fig.3.**) showed a 166-fold improvement in activity against the Hela cancer cell line.[18]

Moreover, in 2022, a series of TP derivatives was reported by *Mohamed et al.*[19] as combretastatin CA- 4 analogs. Notably, compound **10** (**Fig.3.**) showed a potent anti-tubulin activity (IC_{50} = 3.84 μM) compared to CA-4 (IC_{50} = 1.10 μM). Also, the mechanistic studies proved that compound **10** inhibited HCT-116 cells proliferation through inducing apoptosis and halting the cell cycle at the G2/M phase.

In the same year, *Chen et al.* [20] made a structural modification of compound **10** by removing the 5-aryl substitution and replacing the 2-free amino group with a substituted one, leading to the development of a series of TP derivatives. Interestingly, compound **11** (**Fig.3**) showed a five-fold improvement compared with compound **10** against the same three tested cell lines (A549, HeLa, and HCT116 cells)**.** Moreover, compound **11** displayed potent tubulin polymerization inhibitor activity (IC_{50} = 4.9 μM) compared to CA-4 (IC_{50} = 4.20 μM).

At the same time, two studies of various 2,7-disubstituted-TP derivatives were conducted [21,22]. Among them, compounds **12** and **13** (**Fig.3**) were the most active and showed a marked tubulin-inhibiting activity with IC_{50} values of 0.39 μM and 0.45 μM, respectively, compared to CA-4 (IC_{50} = 0.75 μM). Moreover, compound **12** displayed potent antiproliferative activity against HT-29, MDA-MB-231, HeLa, A549, and Jurkat cancer cell lines. Interestingly,

compound **13** displayed potent antiproliferative activity against A549 and HeLa cancer cell lines with IC_{50} of 0.043 μM and 0.038 μM, respectively, compared to CA-4 (IC_{50} of 0.180 μM and 0.004 μM, respectively).

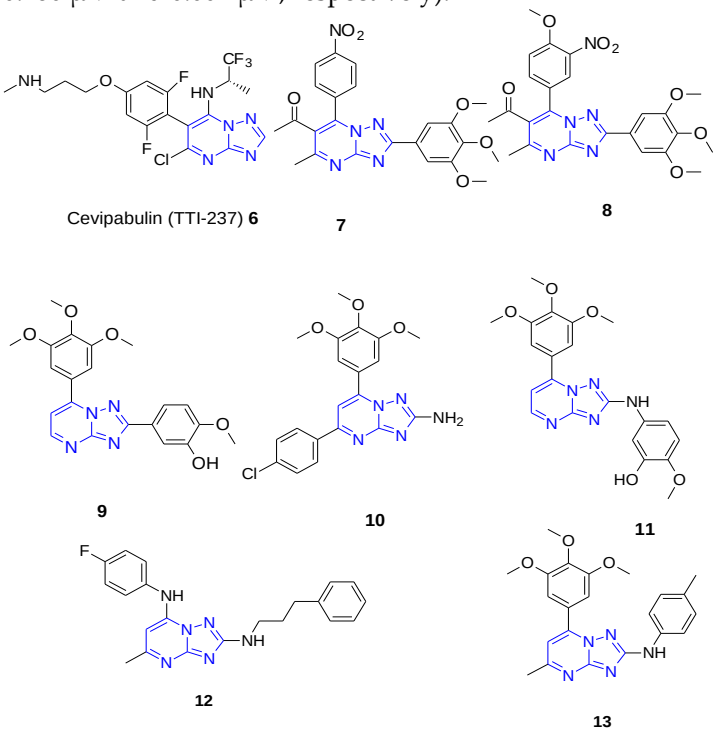


Fig.3. Structures of TP derivatives **6-13** having tubulin polymerization inhibitory activity.

2.1.1.2. Cyclin dependent kinase inhibitors (CDK inhibitors)

Cyclin-dependent kinases are a group of enzymes responsible for cell cycle activation, including metabolism, differentiation, cell division, and transcription through activating G1/M and G2/S transitions, making them a valuable target for developing anti-cancer agents.[23–26] Over the years, researchers have investigated TP derivatives as purine surrogates. For example, seliciclib (Roscovitine, CYC202)[27] **14** (**Fig.4**) is a purine derivative that inhibits multiple CDK enzymes (CDK-1, CDK-2, CDK-5 and CDK-7) through competition at ATP binding catalytic site with ATP. Now, Seliciclib **14** is in phase II clinical trial for treating Cushing disease and reverse hypercortisolism.[28] A medium throughput screening campaign of more than 3000 compounds led to the development of pyrazolopyrimidine derivative **15** as a potent CDK-2 inhibitor with IC_{50} = 1.8 μM. Replacing C3 with nitrogen of compound **15** led to the developing of a TP derivative **16** with lower inhibitory activity against CDK-2. Optimization of SAR of compound **16** led to the development of TP derivative **17** with more potent activity against CDK-2 (IC_{50} = 1.2 μM) and improved selectivity against GSK3-β (**Fig.4**).[29]

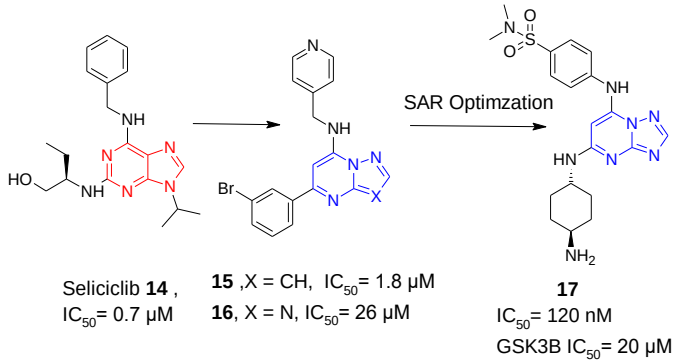


Fig.4. Structures of compounds **14-17** acting as potent CDK inhibitors.

2.1.1.3. Tyrosyl DNA Phosphodiestrase 2 (TDP2) Inhibitors

Topoisomerase II-mediated DNA damage is repaired by TDP2, making cancer cells more resistant to TOPII poisons (doxorubicin and etoposide).[30–32] Thus, TDP2 inhibitors increase cancer cells sensitivity towards TOPII poisons.[33] HTS of more than 1600 molecules led to identifying hit compound (P10A10) **18** as a promising candidate for TDPII inhibition. Hit validation through the resynthesis of compound **19** led to unexpected results showing that this compound is utterly inactive at 100 μM.[34] So, further structural optimization of compound **18** by shifting phenyl substitution from C-7 to C-5 led to the development of compound **19** with promising TDP2 inhibiting activity (IC_{50} = 22 μM) (**Fig.5.**).[35]

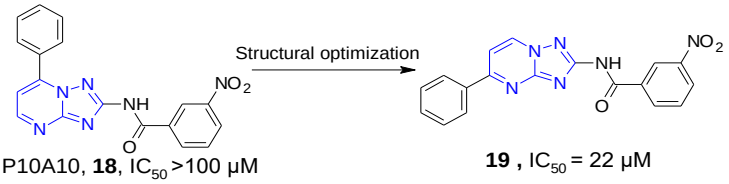
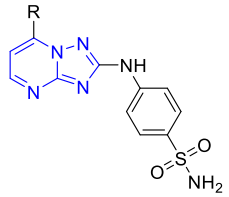


Fig.5. Structures of TP derivatives **18** and **19** acting as TDP2 inhibitors.

2.1.1.4. Carbonic Anhydrase inhibitors (CA inhibitors)

There are seven known CA families in nature, but only the alpha family is expressed in humans (hCAs).[36] Human alpha CA is a group of fifteen enzymes (CA I-CA XV) involved in different physiological processes.[37–40] Notably, CA IX and CA XII are overexpressed in various cancer cell lines but limited in normal tissue, making them valuable targets for developing anti-cancer agents.[36] Different CA inhibitors have been reported. Among them, sulfonamide derivatives were one of the most active classes.[40–42] *Giampietro Viola et al.*[43] identified a class of triazolopyrimidine-sulfaniliamide hybrids as potent CA IX and CA XII inhibitors with K_i in a nanomolar range. Among them, TP derivatives **20** and **21** were the most active compared to acetazolamide (**Fig.6.**).



20, R = 3-Pyridnyl , K_i = 5.1 nM (CA IX), K_i = 8.8 nM (CA XII)
21, R= 2,3,6-triflurophenyl, K_i = 8.6 nM (CA IX), K_i = 5.4 nM (CA XII)
Acetazolimide, K_i = 25 nm (CA IX), K_i = 5.7 nM (CA XII)

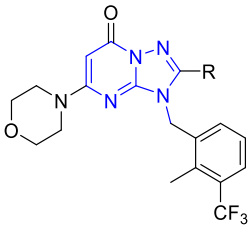
Fig.6. Structures of TP derivatives **20** and **21** acting as potent CA inhibitors.

2.1.2. Signal transduction pathway target

Modifying signaling transduction pathways that control cell growth, motility, division, and death is essential in cancer progression. Multiple inhibitors of signaling transduction pathways, phosphatidylinositol 3-kinases (PI3Ks), paired-box gene 2 (Pax2), and extracellular signal-regulated kinase 3 (ERK3) have been developed as effective anti-cancer treatment recently.

2.1.2.1. PI3K inhibitors

PI3Ks are a group of enzymes involved in inositol phosphorylation, cell metabolism, cell proliferation, and cell survival. Dysregulation of PI3K actions plays an active role in converting normal cells into cancerous ones and inactivating tumor suppressor proteins PTEN. *Sanchez et al.*[44] identified a series of triazolo[1,5-a]pyirimidinone derivatives as potent PI3K inhibitors with enhanced β isoform selectivity. Compounds **22a** and **22b** were the most active, with IC_{50} of 0.4 nM and 0.6 nM, respectively (**Fig.7.**).

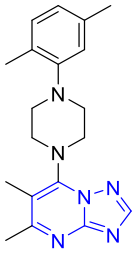


22a, R = -SCH_3, IC_{50} = 0.4 nM
22b, R = CH_3, IC_{50} = 0.6 nM

Fig.7. Structures of TP derivatives **22a** and **22b** acting as potent PI3K inhibitors.

2.1.2.2. Pax2 inhibitors

Pax proteins are a family of DNA-binding proteins essential for the growth of different organs, including the kidney, pancreas, ear, and CNS. Notably, Pax2 is expressed in kidney-developing nephrons but not in adult proximal or distal tubes. On the other hand, it is highly expressed in polycystic kidney epithelia and renal carcinoma. Based on the HTS campaign of more than 69000 compounds performed by *Bradford* and her colleagues to identify potent Pax2 inhibitors, TP derivative (BG-1) **23** (**Fig.8.**) was the most active, exhibiting a potent inhibition of Pax2-positive cancer cells with little effect on Pax2-negative ones.[45]

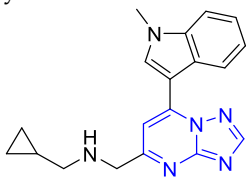


23, IC_{50} = 1.5 μM

Fig.8. Structure of TP derivative **23** acting as potent Pax2 inhibitor.

2.1.2.3. ERK inhibitors

ERK signaling pathways play a significant role in cell growth regulation and are highly expressed in different types of cancers, making them promising therapeutic targets. *Zhang et al.* reported a novel TP series with potent activity against gastric cancer cells MGC-803. Compound **24** (**Fig.9.**) was the most active with IC_{50} = 13.1 μM and displayed potent inhibitory activities on the ERK signaling pathway, resulting in decreased ERK1/2, c-Raf, MEK1/2, and AKT phosphorylation levels.



24

Fig.9. Structure of TP derivative **24** acting as ERK inhibitor.

2.1.3. Ubiquitin-proteasome inhibitors

Hershko, Ciechanover, and Rose won the Nobel Prize in chemistry[46] for the identification of the ubiquitin-proteasome system (UPS). UPS is responsible for the ubiquitination, degradation, and turnover of various proteins necessary for various cellular functions, including cell division, migration, and death, through a triple cascade mechanism.[47] Since the UPS is important for different cell functions and disruption in the cell cycle can lead to oncogenesis, it became an attractive target for researchers to develop new antineoplastic agents.[48]

2.1.3.1. Targeting DCN1-UBC12 interaction

Ubiquitin-protein ligases E3 can be divided into U-box, HECT (homologous to E6-AP carboxy terminus), and RING (interesting new gene). Notably, the RING family contains two subclasses: cullin-containing RING-finger ligases

(CRLs) and other RINGs. Cullin-RING ligases (CRLs) account for nearly 20% of cellular protein degradation through the ubiquitin−proteasome system, and their dysfunction has been observed in many diseases, including cancer. There are five defective cullin neddylation (DCN) isoforms (DCN1−5) in the human genome. Among them, DCN1 is elevated in different types of cancers, including cervical cancer, prostate cancer, colorectal cancer, and laryngeal squamous cell carcinoma.[48] *Wang et al.* reported TP derivative **WS-291**, **25** through HTRF as a hit compound for inhibition of DCN1-UBC12 interaction with an IC_{50} of 5.82 μM. Structural optimization of **WS-291** led to the identification of a more potent inhibitor **WS-383, 26** with an IC_{50} of 0.011 μM (**Fig.10.**).[49]

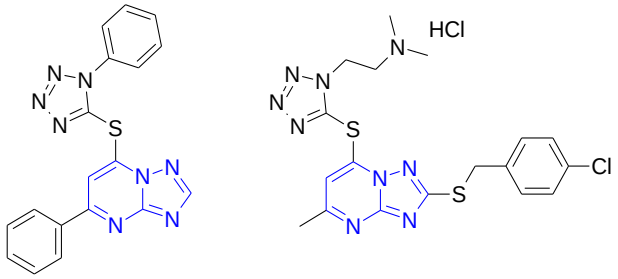


Fig.10. Structures of TP derivatives **25** and **26** targeting DCN1-UBC12 interaction.

2.1.3.2. Targeting RBX1-UBE2M interaction

In 2024, *Ma et al.*[50] identified TP derivative **WS-299, 27** (**Fig.11.**) as a potent antiproliferative agent MGC-803 and HGC-27 cell lines with IC_{50} values of 1.0 μM and 1.8 μM, respectively. Compound **27** exerted its anti-cancer effect by targeting RBX1-UBE2M interaction and inhibiting the CUL3 and CUL5 neddylation modification.

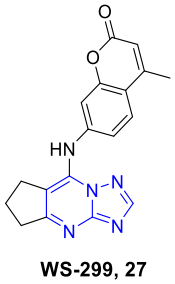


Fig.11. Structure of TP derivatives **27** targeting RBX1-UBE2M interaction.

2.1.4. Epigenetic modifier inhibitors

Epigenetic modification starts with modifying DNA and histone proteins that regulate accessibility and functions, remodeling the basic chromatin unit (nucleosome).[51] These epigenetic modifications control gene expression and have proved crucial in maintaining the malignant process, making them important targets for cancer treatment. Many epigenetic regulators are approved by the FDA, including DNA methyltransferase, isocitrate dehydrogenase 1 or 2, histone methyltransferases, and histone deacetylases or under investigation, such as bromodomain proteins and histone demethylases.

2.1.4.1. LSD1 inhibitors

Lysine-specific demethylase 1 (LSD1) is an enzyme that removes the methyl group from mono-/di-methylated histone 3, lysine 4 (H3K4me1/2), and other methylated nonhistone proteins. Overexpression of LSD1 is noted in various cancers, making it an attractive target. Nine small molecules targeting LSD1 are under clinical investigation, but none of them approved for clinical usage yet owing to severe side effects. *Wang and* his colleagues reported two series of TP derivatives as potent LSD1/KDM1A inhibitors and evaluated their cytotoxic activity against MGC-803, EC109, A549, and PC-9 cell lines. Among the two series, compounds **28-31** (**Fig.12.**) were the most potent LSD1 inhibitor with IC_{50} values of 0.882 μM, 0.154 μM, 1.19 μM, and 0.557 μM, respectively. Interestingly, compounds **28** and **29** enhanced the accumulation of H3K4me1/me2 and H3K9me2 (LSD1 substrates) and inhibited A549 cell migration in a concentration-dependent manner. Also, compounds **28** and **29** increased E-cadherin and claudin-1 expression (two epithelial indicators) and decreased expression of N-cadherin (mesenchymal marker), snail, and slug (transcription markers). On the other hand, compound **32** exhibited potent PC-9 growth inhibition with IC_{50} = 0.59 μM, about 4-fold compared to 5FU, despite having less potent LSD1 inhibitory activity (IC_{50} > 10 μM).[52–55]

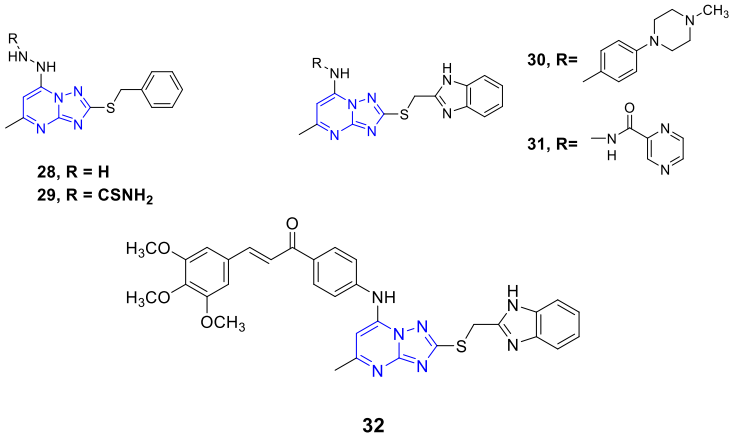


Fig.12. Structures of TP derivatives **28-32** acting as LSD1 inhibitors.

2.1.4.2. BRD-4 inhibitor

Bromodomain containing protein-4 (BRD-4) is an epigenetic reader that is essential for gene expression during the G1 phase. BRD proteins have emerged to play a significant role in the occurrence of different diseases, including malignant tumors, making them attractive targets for researchers to discover new anti-cancer candidates. More than 20 BRD-4 inhibitors have been under clinical trials to treat different types of cancers.[56] Interestingly, TP scaffolds have emerged as possible bio-isostere to the N-acetyl fragment of ε-N-acetylated lysine. TP derivatives **33-35** (**Fig.13.**) have been reported as KAc mimetics and bind within the BRD-4 binding site, making them good inhibitors with IC_{50} of 24 μM, 5 μM, and 2.15 μM, respectively, compared to JQ1 as a positive control (IC_{50} = 0.13 μM). Compound **35 (WS-722)** also induced cell apoptosis and enhanced caspase-3/7 and PARP cleavage of THP-1 cells (IC_{50} = 3.86 μM).[57]

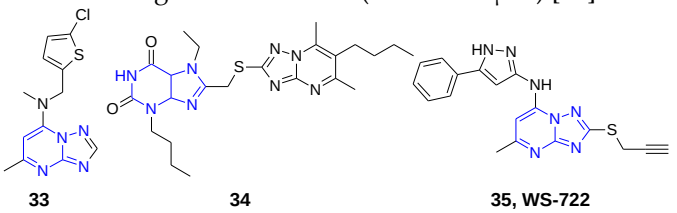


Fig.13. Structures of TP derivatives **33-35** acting as BRD-4 inhibitors.

2.1.5. Targeting tumor microenvironment

Tumor microenvironment (TME) has been reported as a crucial controller of cancer growth, metastasis, and multidrug resistance. TME includes tumor vasculature, immune cells, stomal cells, and extracellular matrix. Methionine aminopeptidase-2 (MetAP-2) is a key enzyme believed to play a crucial role in tumor angiogenesis and, therefore, tumor cell multiplication and spread. Screening campaign for MetAP-2 inhibitors led to identifying purine analogue **36** as a potent inhibitor of MetAP-2 with IC_{50} equal to 0.23 μM. Further optimization of compound **36** by replacing the purine ring with TP scaffold led to the development of TP derivative, **37** (**Fig.14.**) which showed more potent inhibition activity against MetAP-2 (IC_{50} = 0.038 μM) and good physiochemical profile.[58]

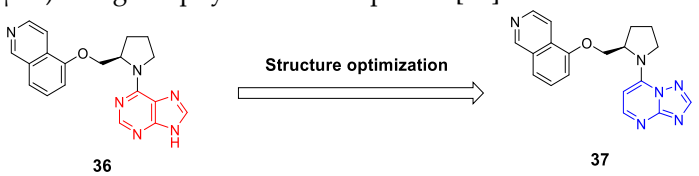


Fig.14. Structures of compounds **36** and **37** targeting tumor microenvironment.

2.1.6. Multidrug resistance (MDR)

A common challenging complication developed in most patients taking chemotherapeutic agents is multidrug resistance (MDR). MDR occurs for different reasons, of which ATP-binding cassette (ABC) transporters that transport drugs outside tumor cells are believed to be the most prominent factor. TP derivatives have emerged as a promising candidate to reverse MDR by inhibiting ATP-binding cassette subfamily B member 1 (ABCB1), which enhances drug efflux outside cancer cells and reduces drug intake. *Liu et al.* reported different TP series acting as potent ABCB1 inhibitors; among them, compounds **38** and **39** (**Fig.15.**) were the most active with IC_{50} values equal to 22 nM and 3.67 nM, respectively.[59,60]

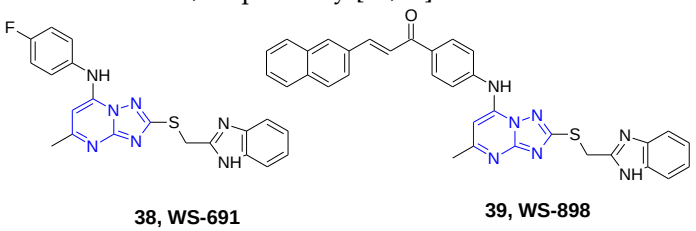


Fig.15. Structures of TP derivatives **38** and **39** acting as ABCB1 inhibitors.

2.2. Central nervous system

In recent years, triazolopyrimidine has emerged as a prominent scaffold in developing candidates for treating different CNS diseases. TP analogs exert their action through one of the following:

a- Inhibition of Acetylcholine Esterase
b- Stabilizing Microtubules
c- Inhibition of PDE2A

2.2.1. Acetylcholine esterase inhibitors

Three studies conducted by *Jayaram et al.* led to the development of TP hybrids as a promising inhibitor of acetylcholine esterase for the treatment of Alzheimer's disease. These hybrids exert their action through dual targeting of the catalytic active site and the peripheral anionic site through π-π interaction with important residues (Tyr70 and Trp279), which play an important role in the regulation of the entry of substrate to the binding site of AChE. Among the synthesized three series, compounds **40-43** (**Fig.16.**) showed the most potent inhibiting activity of AChE with IC_{50} = 0.042 μM, 0.065 μM, 0.092 μM, and 0.160 μM, respectively, compared to reference compound tacrine (IC_{50} = 0.13 μM). Also, *in silico* ADMET profiling showed that these derivatives possess drug-like properties as well as low toxicity. Based on these results, SAR revealed that the presence of the triazolopyrimidine or other isosteric groups is important for π-π interaction with the PAS residue of AChE, a linker (Piperazine) interacts with the aromatic gorge of AChE and a heterocyclic moiety intercalates

between sheets of amyloid β (quinoline or triazine or pyrimidine) are essential for inhibiting activity.[61–63]

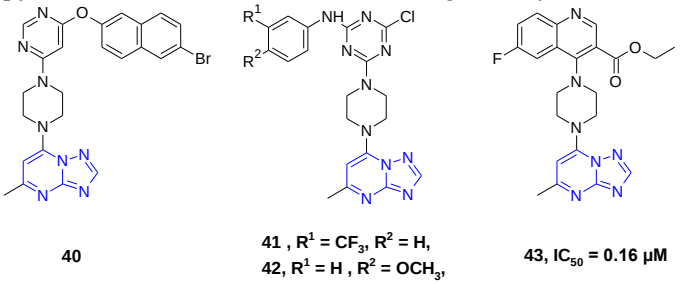


Fig.16. Structures of TP derivatives **40-43** acting as AChE inhibitors.

2.2.2. Microtubule stabilizing agents

Microtubule active agents have versatile applications in developing promising candidates for treating different diseases, including neuropathies and cancer. *Carlo Ballatore and his colleague*s conducted several studies to understand how MT active TPs either enhance the stabilization of MT or disrupt MT integrity. These studies revealed that TP analogs with an alkoxy side chain at position number 4 of the fluorinated phenyl ring destabilize MT assembly, whereas other TP analogs lacking the alkoxy side chain stabilize MT (compounds **44-46, Fig.17.**). Alzheimer's disease and other neurodegenerative diseases are characterized by the presence of insoluble inclusions of tau protein, which is associated with axonal MT in the brain, leading to loss of axonal density and axonal dystrophy. Based on these facts, they examined MT stabilizing TP analog **44** (**CNDR-51657**) (**Fig.17.**) with a low dose (3-10 mg/kg) in the mouse tauopathy model, which is a low dose (3-10 mg/kg) for 3 months enhanced MT stabilization, decreased tau pathology, and reduced axonal deflects.[64–67]

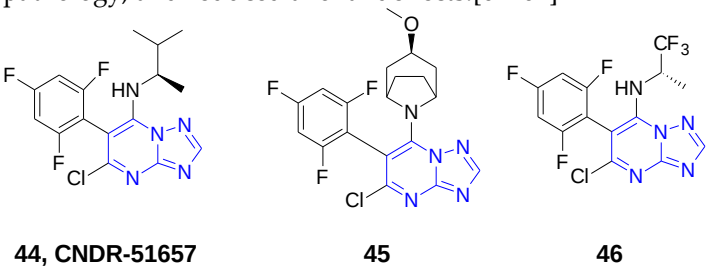


Fig.17. Structures of TP derivatives **44-46** acting as microtubule stabilizing agents.

2.2.3. Inhibition of PDEA2

Phosphodiesterase (PDE) enzymes are catabolic enzymes encoded by 21 genes and are classified into twelve families (PDE1-PDE12). PDEs are responsible for the hydrolysis of cAMP and cGMP to the corresponding inactive AMP and GMP, respectively. PDE2A is expressed in the brain, especially in hippocampus, striatum and cortex. Thus, its inhibition led to an increase in intracellular cAMP and cGMP, which play a key role in neuroplasticity and correlate to learning and memory.[68] An important patent application of 566 (1,2,4)-triazolo(1,5-a)pyrimidine analogs was exemplified by Dart Neuroscience. Among them, 192 compounds were reported to have pIC_{50} less than 7 for PDE2A, but selectivity towards other PDEs wasn't disclosed in this patent (Compounds **47-49 (Fig.18)** are representative examples of the most active TP derivatives). Further structural optimization led to the identification of the lead compound **50, DNS-8254**, as a highly selective PDE2A inhibitor with IC_{50} of 8 nM and showed significant memory-enhancing effects and favorable pharmacokinetic properties *in vivo*.[69] In 2020, *Tresaden et al*. reported a hit to lead exploration of 1,2,4-triazolo(1,5-a)pyrimidine derivative **51** (**Fig.18.**) through HTS campaign (HTS) as a potent inhibitor of PDE2A enzyme (IC_{50} = 1.3 nM) and 100 fold selective over the other PDE enzymes.[70]

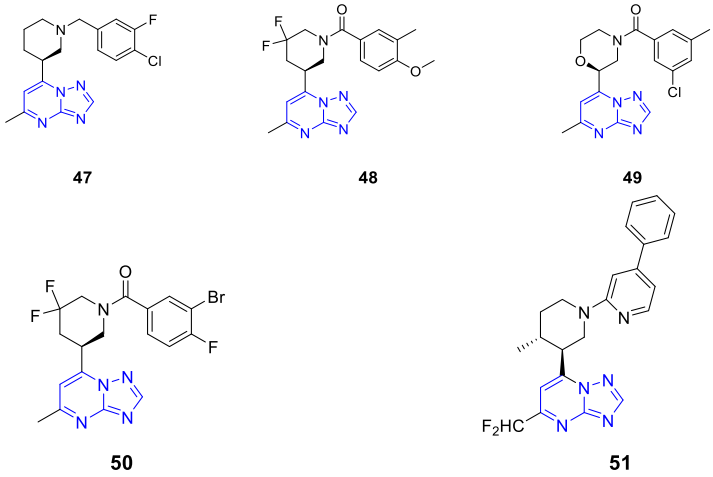


Fig.18. Structures of TP derivatives **47-51** acting as PDE2A inhibitors.

2.3. Anti-infectious agents

TP scaffold represents a good pharmacophore for developing different candidates that have been acting as potent anti-infectious diseases over recent years. Different TP derivatives have been reported as antibacterial, antiparasitic, and antiviral agents.

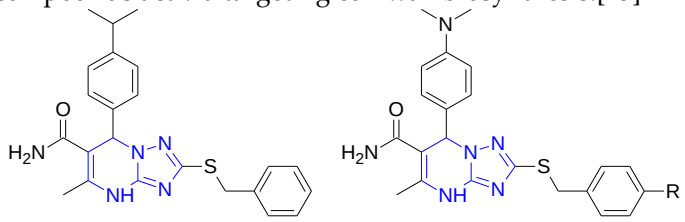
2.3.1. Anti-bacterial agents

Despite essramycin **1**[71] was the first TP derivative as an antibacterial agent, recent studies revealed that essramycin believed to be devoid of any antibacterial activities.[72,73] In literature, many TP derivatives have been reported as potent antibacterial agents with a broad spectrum against Gram-positive and Gram-negative bacteria.[74–80] Important results can be summarized that the most active

compounds may act through different targets, including cell-wall biosynthesis, DNA gyrase enzyme, and acetohydroxy acid synthase enzyme (AHAS).

2.3.1.1. Targeting cell-wall biosynthesis

In 2015, *Wang* et al. screened 118 selected compounds for their antibacterial activity against the ESKAPE panel of organisms. This screening identified TP derivatives **52** as a lead candidate that showed good antibacterial activity against *Enterococcus faecium* with MIC of 8 μg/mL while no antibacterial activity against the other bacteria in the ESKAPE panel. *E. faecium* infections are resistant to the most commonly used antibiotics, accounting for 25% of total enterococci infections in intensive care units. Furthermore, *Wang* et al. synthesized 67 analogs of compound **52** and screened them for their activity against *E. faecium*. Compounds **53** and **54** (**Fig.19.**) were the most active, with MIC of 4 μg/mL superior to vancomycin (MIC = 64 μg/mL). Macromolecular synthesis assays revealed that these compounds act via targeting cell-wall biosynthesis.[75]

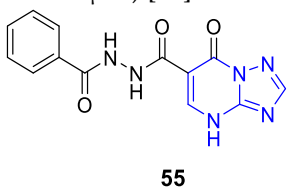


52 **53, R = H**
54, R = -CN

Fig.19. Structures of TP derivatives **52-54** targeting cell-wall biosynthesis.

2.3.1.2. Targeting DNA Gyrase

In 2019, *Abd El-Aleam* et al. reported a series of TP as potent antibacterial agents against different Gram-positive and Gram-negative bacteria with MIC values from 0.25 μg/mL to 2.0 μg/mL acting through inhibition of DNA Gyrase enzyme. TP derivative **55** (**Fig.20.**) was the most active DNA Gyrase inhibitor with IC_{50} of 0.68 μM superior to ciprofloxacin (IC_{50} = 0.85 μM).[77]

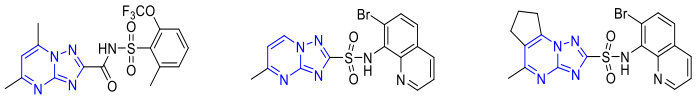


55

Fig.20. Structures of TP derivative **55** acting as DNA gyrase inhibitor.

2.3.1.3. Targeting Acetohydroxyacid Synthase enzyme (AHAS)

AHAS enzyme is an anabolic enzyme that plays a fundamental role in branched-chain amino acid biosynthesis, which is important for the survival of microbes. Interestingly, branched-chain amino acid biosynthesis is absent in humans, making them an important target for developing effective and safe antitubercular agents. In this context, HTS campaigns, SAR studies, and molecular docking were done to develop novel potent AHAS inhibitors as possible candidates for the treatment of tuberculosis. *Patil et al*. designed a series of TP derivatives as potent AHAS inhibitors by hybridizing known AHAS inhibitors such as sulfonyl urea and triazolopyrimidine scaffold. The synthesized compounds showed promising anti-TB activities with MICs ranging from < 0.03 μg/mL to 2.0 μg/mL and AHAS inhibition activity pIC_{50} = 5.81–7.75. TP derivative **56** (**Fig.21.**) was the most active antitubercular agent with MIC < 0.03 μg/mL and AHAS pIC_{50} = 7.75.[74] In 2016, *Moon-Young Yoon et al*. made HTS of more than 6800 compounds to identify potent inhibitors of MTB-AHAS. From this HTS, five TP derivatives emerged as promising MTB-AHAS inhibitors with IC_{50} ranged from 0.4 μM to 1.24 μM. Among them, compounds **57** and **58** (**Fig.21.**) exhibited marked pharmacological activities against different TB strains, including multidrug-resistant (MDR-TB) and extensively drug-resistant (XDR-TB) strains with MIC = 0.5 μM and 2 μM, respectively, as well as showing good safety against mammalian cell lines.[76]



56 **57** **58**

Fig.21. Structures of TP derivatives **56-58** acting as AHAS inhibitors.

2.3.2. Anti-viral agents

2.3.2.1. Anti-influenza activity

To date, the Influenza virus is considered a potential threat all over the world, accounting for a lot of deaths, especially in high-risk people. Few therapeutic agents, including the yearly reformulated vaccine, M2 ion channel inhibitors, neuraminidase inhibitors, and RNA-dependent RNA polymerase subunits PA-PB1 interaction disruptors, are available. X-ray crystallography revealed the interaction between PA-PB-1 subunits, which enabled a group of Italian researchers to make a virtual screening of 3 million compounds, leading to a hit pyrazolo[1,5-*a*]pyrimidine derivative **59** (**Fig.22.**) which was confirmed to inhibit polymerase subunits interaction *in vitro* with IC_{50} = 27.2 μM. Further structural modification by replacing the pyrazole-

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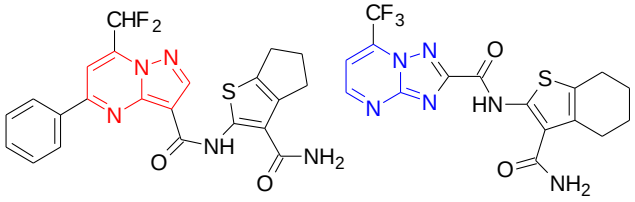
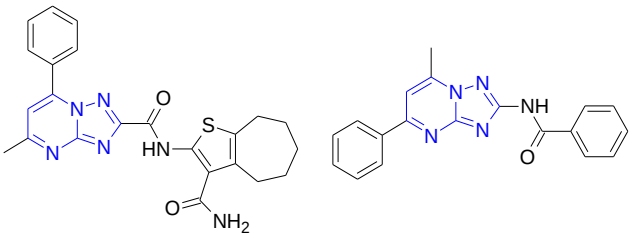
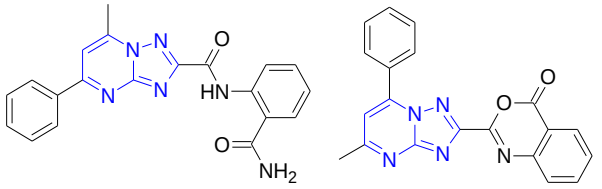
ring with a 1,2,4-triazole ring led to the developing of more potent compounds with improved *in vitro* and *in vivo* activities. Among other studies made by the same group of researchers, TP derivatives **60-64** (**Fig.22.**) showed the highest inhibitory activities of PA-PB1 with IC_{50} = 1.1- 26 μM, and a good safety profile.[81–84]



59, PA-PB1 IC_{50}= 27.2 μM **60, PA-PB1 IC_{50}= 7.5 μM**



61, PA-PB1 IC_{50}= 1.1 μM **62, PA-PB1 IC_{50}= 26 μM**

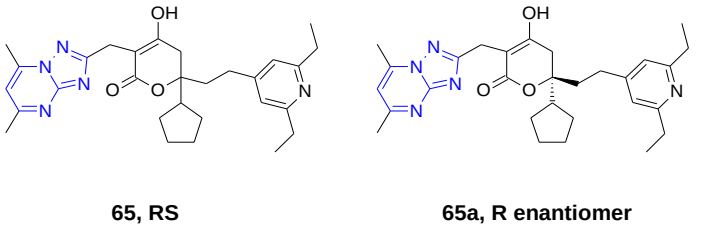


63, PA-PB1 IC_{50}= 7.5 μM **64, PA-PB1 IC_{50}= 19.5 μM**

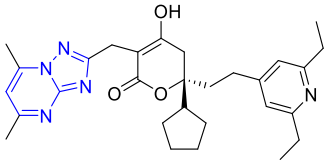
Fig.22. Structures of TP derivatives **59-64** acting as PA-PB1 inhibitors.

2.3.2.2.2. Anti-HCV activity

HCV is one of the main causes of chronic liver diseases and searching for safe and effective drug is significant. HCV nonstructural protein 5B (NS5B) is an RNA-dependent RNA polymerase that has the main role of viral replication. It differs from human DNA and RNA polymerases, making it an important therapeutic target for developing anti-HCV candidates. HTS campaign made by Pfizer for structural optimization of allosteric HCV NS5B dihydropyrone inhibitors led to the development of TP derivatives with marked potent HCV NS5B polymerase inhibition activity (IC_{50} = 0.007 μM - 0.016 μM). Among them, TP derivative **65** (**Fig.23.**) showed potent NS5B inhibition activity with IC_{50} = 0.016 μM, which then separated into its two enantiomers **65a, Filibuvir**, and **65b** with IC_{50} = 0.007 μM and 0.012 μM respectively.[85] The R enantiomer **65a, Filibuvir,** reached phase II clinical trials for HCV treatment, but the investigation was discontinued in 2013 for strategic reasons.



65, RS **65a, R enantiomer**



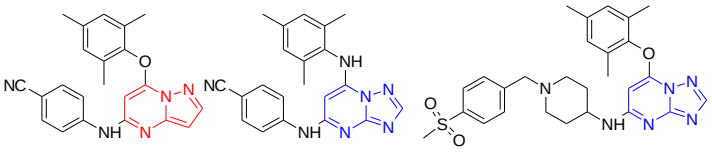
65b, S enantiomer

Fig.23. Structure of anti-HCV TP derivative **65** and its enantiomers **65a** and **65b.**

2.3.2.3. Anti-HIV activity

HIV-1 reverse transcriptase is the key enzyme involved in HIV replication, making it one of the crucial targets for the treatment of HIV/ AIDS. Three studies conducted by *Xin Yong Liu et al.* to identify non-nucleoside reverse transcriptase (NNRTI) led to the development of a series acting as a potent inhibitor of HIV.[86–88] The first study identified a series of pyrazolopyrimidine derivatives acting as potent anti-HIV-1 with EC_{50} from 0.07 μM to 5.98 μM. Pyrazolopyrimidine derivative **66** (**Fig.24.**) was the most active with EC_{50} = 0.07 μM.[86]

In the other two studies, structure-guided core refining approaches and molecular docking studies led to the development of a series of TP derivatives acting as potent wild-type HIV-1 III_B inhibitors. TP derivatives **67** and **68** (**Fig.24.**) were the most active against wild-type HIV-1 III_B with EC_{50} = 0.0200 mM and 0.0081 mM, respectively, and showed weak to moderate activity against K103N/Y181C double resistant mutant strain of HIV-1 with EC_{50} = 7.6 mM and 13 mM respectively. These compounds are believed to act by interacting with the diaryl pyrimidine allosteric site located 10 Å away from the reverse transcriptase catalytic site.[87,88]



66 **67** **68**

Fig.24. Structures of compounds **66-68** acting as anti-HIV.

2.3.3. Anti-parasitic agents

Recently, TP derivatives have been reported as a promising candidate for treating different infections caused by various parasites, mainly kinetoplastid and plasmodium parasites.

2.3.3.1. Activity against Kinetoplastid parasites

Many infections such as leishmaniasis, Chagas disease, and African sleeping sickness, are caused by *L. donovani*, *T. cruzi*, and *T. brucei* kinetoplastid parasites, respectively. Screening of more than 3 million compounds led to the development of a hit azabenzoxazole derivative **69 (GNF5343)** (**Fig.25.**). Structural optimization of compound **69** by replacing azabenzoxazole with TP scaffold led to the development of a series of TP derivatives with broad spectrum activity against different kinetoplastid parasites with more favorable ADME-PK properties. TP derivatives **70-72** (**Fig.25.**) were the most active with EC_{50} = 350 μM, 71 μM, and 15 μM against *L. donovani*, EC_{50} = 55 μM, 16 μM, and 120 μM against *T. cruzi*, and 79 μM, 22 μM, and 70 μM against *T. brucei*, respectively.[89]

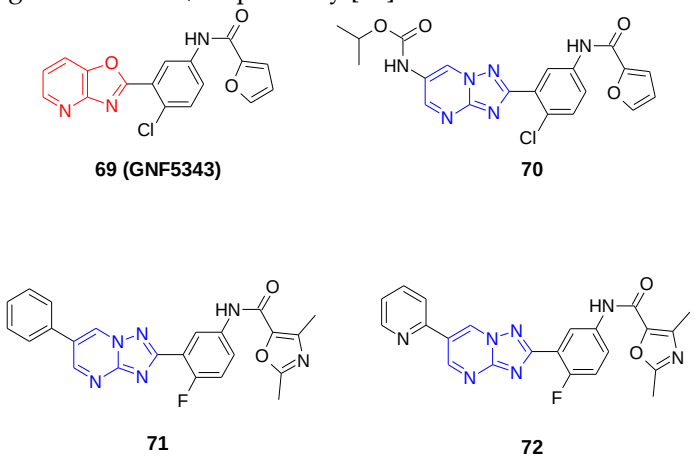


Fig.25. Structures of compounds **69-72** acting against kinetoplastid parasites**.**

2.3.3.2. Antimalarial agents

Malaria is one of the most common causes of death around the world, especially in tropical and subtropical regions (> 90% of cases were found in Africa). Malaria is a mosquito-borne infection caused by one of four types of Plasmodium species: P. falciparum, *P. vivax*, *P. ovale*, and *P. malariae*, resulting in severe illness and even death if not treated well within one day of infection. Malaria is spread by the bite of female *Anopheles* mosquitoes. Plasmodium dihydroorotate dehydrogenase (*p*DHODH) is one of the key enzymes involved in *de novo* pyrimidine biosynthesis and has been validated clinically as a promising drug target for developing novel antimalarial agents. In this context, various *p*DHODH inhibitors based on different scaffolds have been reported in the last two decades and are known as **DSM** compounds. Among them, TP derivatives **73 (DSM1)** and **74 (DSM2)** were developed from the HTS campaign as potent *p*DHODH inhibitors with IC_{50} values of 0.047 μM and 0.056 μM, respectively.[90] X-ray studies of these compounds showed that the TP ring binds to a polar region (H-bond pocket) while the hydrophobic pocket is occupied by the naphthyl or anthranyl substituent. Structure-guided medicinal chemistry approaches and HTS efforts led to the development of different analogs of **DSM1** with more potent *p*DHODH-inhibiting activities and more favorable ADME properties. As examples, TP derivatives **75 (DSM267)**[91], **76 (DSM338)**[92], **77 (DSM265)**[93], **78 (DSM421)**[94], and **79 (DSM422)**[95] with IC_{50} values equal to 0.038 μM, 0.022 μM, 0.033 μM, 0.053 μM, and 0.0046 μM, respectively (**Fig.26**). Interestingly, **DSM265 (77)** showed excellent *in vivo* anti-parasitic activity against both *P. falciparum* and *P. vivax* and reached phase IIa clinical trials.

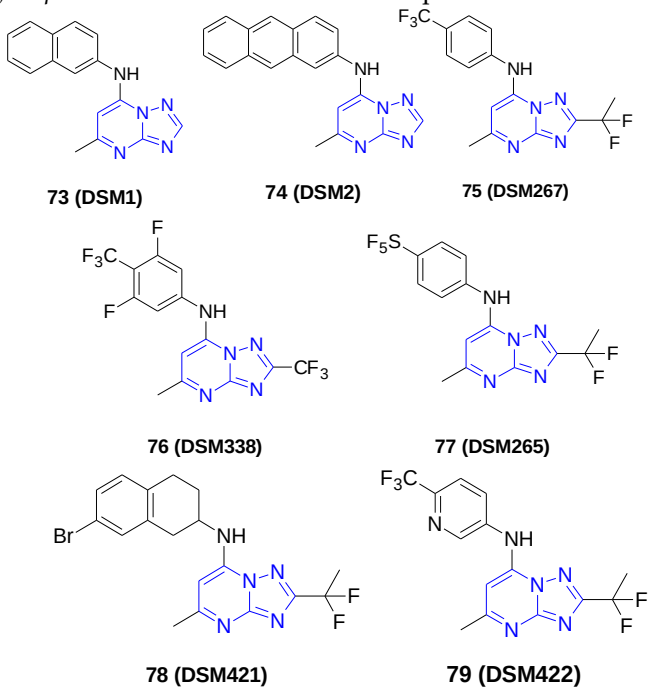


Fig.26. Structures of TP derivatives **73-79** acting as antimalarial agents**.**

3. Conclusion

The 1,2,4-Triazolo[1,5-a]pyrimidine scaffold emerged as a prominent scaffold in designing novel compounds acting as promising drug candidates for the treatment of several diseases.

Also, the development of pharmacologically active TP analogues has been accelerated recently, with many of these analogues displaying drug-like properties. This review summarizes the most important application of TP in medicinal chemistry and illustrates their interactions with several targets for their diverse biological activities.

Ethical consideration: All the participants in this study gave their informed permission.

Conflicts of Interest

No conflicts of interest are disclosed.

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