Bioorganic & Medicinal Chemistry Letters 23 (2013) 6805–6810

Contents lists available at ScienceDirect

Bioorganic & Medicinal Chemistry Letters

journal homepage: www.elsevier.com/locate/bmcl

Design, synthesis and evaluation of 6-(4-((substituted-1*H*-1,2,3-triazol-4-yl)methyl)piperazin-1-yl)phenanthridine analogues as antimycobacterial agents

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ARTICLE INFO

Article history:
Received 23 July 2013
Revised 25 September 2013
Accepted 7 October 2013
Available online 14 October 2013

Keywords:
Phenanthridine
Piperazine
Triazole
Click chemistry
Anti-tubercular activity

ABSTRACT

Focus in this Letter is made to design and synthesize a series of nineteen new 6-(4-((substituted-1*H*-1,2,3-triazol-4-yl)methyl)piperazin-1-yl)phenanthridine analogues employing click chemistry and evaluated for their anti-tubercular activity against *Mycobacterium tuberculosis* $H_{37}Rv$. Among the tested compounds, **7f** and **7j** exhibited good activity (MIC = 3.125 μg/mL), while **8a** displayed excellent activity (MIC = 1.56 μg/mL) against the growth of *M. tuberculosis* $H_{37}Rv$. In addition, **7f**, **7j** and **8a** compounds were subjected to cytotoxic studies against mouse macrophage (RAW264.7) cell lines and the selectivity index values are **>15** indicating suitability of compounds for further drug development.

Tuberculosis (TB) is an infectious disease caused by the bacillus *Mycobacterium tuberculosis* (MTB). It typically affects the lungs (pulmonary TB) but can affect other sites as well (extrapulmonary TB). In general, a relatively small proportion of people infected with MTB will go onto develop TB disease[1]; two factors mainly associated with the spread of TB are human immunodeficiency virus (HIV) infection and the emergence of MTB strains that are resistant to one or more drugs. However, in recent times population of TB patients caused by MTB are increasing in an alarming rate, revealing ineptitude of currently available medicine in the market. Besides effective implementation of Directly Observed Treatment Short course (DOTS), perceptible transformation could be accounted to emergence of multidrug resistant (MDR) and extensively drug resistant (XDR) mycobacterium strains.[2] It is estimated that one-third of the 42 million individuals infected with HIV are coinfected with MTB; most people infected with HIV develop TB as the first manifestation of acquired immunodeficiency syndrome (AIDS). The presence of MDR-TB and XDR-TB can be treated with extended chemotherapy (approximately two years). With an extended treatment period, however, patients have an increased risk of toxicity and the treatment costs are approximately 100 times higher than the typical treatment of TB (which is conducted for six to nine months).[3,4] Also, microbial pathogens contrive their outer cell wall surfaces making it as a complex protective barrier to defend from the effect of antibiotics, radical ion species, and degradative enzymes.[5] The thrust to combat this infectious disease led researchers across the globe to look for novel potential chemotherapeutic agents which remain the cornerstone of patient management.

Heterocyclic motifs have been much exploited in drug discovery development owing to their ample biological spectrum. Mainly, 1,2,3-triazoles have been postulated to generate a nonclassic bioisostere of amide bond[6,7] which is an essential feature to increase binding affinity towards receptor. Much attention have been paid to click chemistry arena due to easily accessible novel complex and diversified heterocycles using environmentally benign and relatively inexpensive catalyst and starting materials. 1,2,3-Triazoles are identified as antifungal, anticancer, antiprotozoal, antiphotoaging, HIV type-1 protease inhibitor, β-lactum antibiotic, histone deacetylase inhibitor,[8–12] etc. Some of the drugs based on 1,2,3-triazoles which are currently in use are depicted in Figure 1.[13]

On the other hand quinoline cores are well known classical heterocyclic backbone in many natural products. The wide range of physiological activities[14,15] and trend of effortless accessibility of

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http://dx.doi.org/10.1016/j.bmcl.2013.10.016

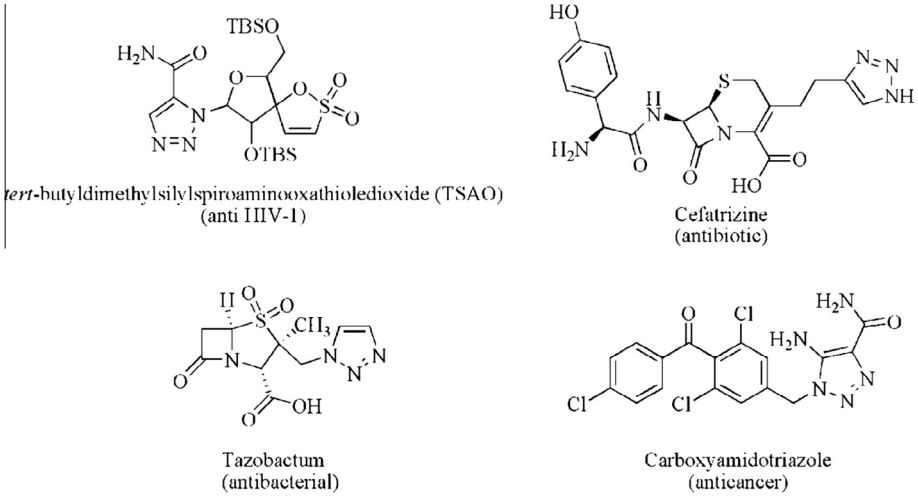

Figure 1. Drugs currently in use based on 1,2,3-triazole skeleton.

quinoline framework draws quick attention of many chemists and biologists. One of the quinoline moieties, Bedaquiline was approved for use in TB treatment[16] is depicted in Figure 2. Sumesh et al., synthesized 1-(2-(3-fluorophenyl)-4-hydroxyquinolin-3-yl)-3-phenylurea (**AA**) (MIC = 0.625 μg/mL) in which presence of aryl ring at 2nd position of quinoline framework exhibited very good anti-tubercular activity than Isoniazid.[17] R.S. Upadhyaya et al., synthesized indeno[2,1-*c*]quinoline derivatives (**BB**) (MIC = 1.56 μg/mL) where 2nd position of quinoline is tailored to 2-pyridyl piperazine.[18] Thomas et al., synthesized 1-(4-((1-(6-methoxy-2-methylquinolin-4-yl)-1*H*-1,2,3-triazol-4-yl)methyl) piperazin-1-yl)ethanone (**CC**) (MIC = 0.625 μg/mL) where introduction of amidopiperazine to the quinolin-4-yl-1,2,3-triazoles framework showed significant activity than isoniazid.[19] As part of our ongoing research on TB program[20] we exploit the advantage of above three heterocycles and designed a strategy to tailor the essential pharmacophores in a single framework and synthesized new 6-(4-((substituted-1*H*-1,2,3-triazol-4-yl)methyl)piperazin-1-yl) phenanthridine derivatives as depicted in Figure 3. Some of the 1,2,3-triazole based anti-tubercular agents are depicted in Figure 4.[3,21–25]

In this Letter, we synthesized 6-(4-((substituted-1*H*-1,2,3-triazol-4-yl)methyl)piperazin-1-yl)phenanthridine derivatives as sketched in Figure 5. We adopted reported procedure with slight modification to prepare 6-Chlorophenanthridine (**4**)[26,27], then 6-(piperazin-1-yl) phenanthridine (**5**)[28] was synthesized by microwave irradiation at 150 °C for 20 min using Biotage initiator with a pre-stirring of 30 s and stirring rate at 600 rpm.

Compound **6** was obtained by heating **5** with propargyl bromide (80% in toluene) in the presence of triethylamine (TEA) using *N,N*-dimethylformamide (DMF) as solvent.[29] The title compounds were synthesized from **6** by means of click chemistry employing catalytic amount of $CuSO_4{\cdot}5H_2O$ and sodium ascorbate in 1:2 ratio of water and *tert*-butanol to get desired compound **7a–q**.[30] While catalytic amount of copper(I)-thiophene-2-carboxylate (CuTC) and toluene as solvent was used to synthesize the compounds **8a–b**.[31] All the title compounds displayed multiplet in the range 2.75–2.95 ppm and 3.45–3.65 ppm corresponding to piperazine ($-CH_2-$) protons, singlet in the range 3.85–4.00 ppm corresponding to methylene proton, and proton of 1,2,3-triazole ring resonated in the range 7.8–8.2 ppm. Both analytical and spectral data (^{1}H NMR, ^{13}C NMR, and HRMS) of all the synthesized compounds were confirmed and employed further for their evaluation.

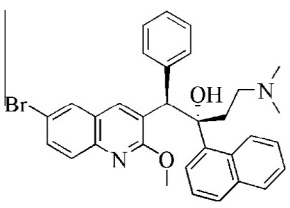

Figure 2. Structure of Bedaquiline.

All the synthesized compounds were tested for their ability to inhibit the growth of MTB $H_{37}R_V$ by Microplate Alamar Blue Assay (MABA).[32] Isoniazid and Rifampicin were used as the positive drug standard. The in vitro antimycobacterial test results of title compounds are tabulated in Table 1 as minimum inhibitory concentration (MIC) and the activity ranges between 1.56 and >3.125 μg/mL. Compounds with MIC $\leqslant$3.125 μg/mL were further subjected to cytotoxicity studies. Amongst the series, compounds **7f** and **7j** (with *p*-methoxy and *m*-chloro substituent respectively), inhibit 99% growth of MTB H_{37}Rv strain at a concentration 3.125 μg/mL. Nevertheless, compound **8a** with sulfonyl functional group sandwiched between five-membered 1,2,3-triazole and phenyl group, emerged as a promising candidate by inhibiting 99% growth of MTB H_{37}Rv strain at a concentration 1.56 μg/mL.

Among the synthesized compounds, electron releasing groups like ethyl and methyl exhibited moderate anti-tubercular activity whereas 1,3-benzodioxole and methoxy at *meta* position had no effect on the activity spectrum. Notably, the introduction of methoxy (**7f**) at *para* position improved the activity by 15 folds (MIC = 3.125 μg/mL). Presence of chloro group (**7j**) at *meta* position (MIC = 3.125 μg/mL) exhibited increase in activity by eight and fourfolds compared to same group at *para* and *ortho* positions respectively. Replacing with bromo group had less affect on the activity spectrum. When electron withdrawing fluoro group was introduced not much change in the activity was observed. Trifluoromethyl group at *meta* position exhibited moderate activity (MIC = 12.5 μg/mL). Hopping to nitro group improved the activity by twofolds (MIC = 6.25 μg/mL). Eventually, we intended to sandwich a sulfonyl group between triazole and the aromatic unit to fetch compounds **8a** and **8b**. This trajectory conferred **8a** as promising ligand of interest with MIC 1.56 μg/mL. Antimycobacterial activity profile suggests that, functional group which has ability to act as hydrogen bond acceptor preferably through its lone pair is essential which might attribute to the enhanced binding interactions.

The active compounds, **7f**, **7j** and **8a** were subjected to in vitro cytotoxicity studies against mouse macrophage (RAW264.7) cell lines.[33] The IC_{50} and selectivity index (SI) values are tabulated in