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Synthesis of Substituted Pyrazole Derivatives: Evaluation of their Anti-Mycobacterial Activity

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Abstract

Various highly substituted pyrazoles were synthesized from the corresponding starting material using HATU reagent. We produce these biologically interesting heterocycles in high yields. All the synthesized compounds are tested against anti-mycobacterial activity. Among them, 9, 10, 12 and 25 are identified as lead molecules. In particular, 9, and 12 are found to display promising activity.

Keywords: Pyrazoles; Heterocycles; Anti-mycobacterial activity

Introduction

Tuberculosis (TB) is a traditional disease caused by infection with Mycobacterium tuberculosis; it is a serious public health issue due to its risk of person-to-person transmission, and high level of morbidity and humanity. The World Health Organization (WHO) estimates 11.4 million people worldwide are infected with both Mycobacterium tuberculosis (Mtb) and HIV. Currently, there are approximately 8 million new infections and 3 million deaths attributed to *M. tuberculosis* annually [1,2]. One of the major problems associated in comprehensive control of TB is that the restart of the disease in patients who carry a latent syndrome, in which the bacteria is in slow budding or non-growing state and is refractory to treat with predictable anti-TB drugs [3]. Directly observed treatment (DOT) is presently practicing for standard TB chemotherapy. It is well known that the resistance levels are poor in the areas with a strongly performing DOTS programs. However, various drugs available in the market cannot be used for prolonged times due to diverse side effects. Therefore, the development of new and safe anti-TB drugs is in high demand. The major investigation on sEH inhibitors focused on urea, amide, amino-heterocycles and carbamate derivatives, but research on new compound structures is limited. Heterocycle Pyrazole [4], triazole [5], benzofuran [6,7], benzoxazole [8] etc. derivatives are constitute an interesting class of organic compounds, which are associated with diverse chemical and pharmacological properties. The pyrazole derivatives are also reported as inhibitors of HIV-1 reverse transcriptase [9], sodium-hydrogen ion exchanger NHE-1 [10] and dipeptidase IV (DPP-IV) inhibitors [11]. Pyrazoles are known to have various chemotherapeutic activities like, antimicrobial [12-20], free radical scavenging [21], anti-inflammatory [22-24], analgesic, antipyretic and antiviral [25,26]. The literature survey revealed that some pyrazoles are implemented as antileukemic [27-29], antitumor [30-32], and anti-proliferative agents, besides their capacity to exert remarkable anticancer effects through inhibiting different types of enzymes that play significant role in cell division.

Design and Synthesis

Information on the common properties of the binding groups is essential for resolving the type of inhibitor binding to the target protein. We had previously designed and developed various classes of inhibitors as mycobacterial GyrB inhibitors utilizing the concept of molecular hybridization. The preliminary structure-activity profiling studies of these leads provided valuable information regarding the basic structural requirements for achieving selective inhibition of mycobacterium GyrB. An imperative from our previous research efforts revealed the importance of hydrophobic interactions in bringing specificity toward the mycobacterial GyrB protein. These findings were equally supported by the crystallographic characterization of the amino pyrazinamide analogs to GyrB protein by researchers from AstraZeneca and reported that the presence of a unique hydrophobic pocket in the active site brought specificity toward the mycobacterial GyrB protein. Having understood the important structural requisite for bringing about specificity and potency toward the mycobacterial GyrB domain, to deliver a novel scaffold/lead with better antimycobacterial activity via inhibition of the gyrase domain. The design strategy utilized for developing the inhibitor has been sketched in Scheme 1. Thus a set of twenty four compounds in this series were designed and synthesized and as presented in Table 1. The designed ligand was constructed by a simple and straightforward strategy as shown in Scheme 1. To prepare phenyl pyrazol based leads (compounds 5-26), the ligands were assembled by following the protocol depicted in Scheme 1. Scaffold 1-(3-methyl-1-phenyl-1H-pyrazol-5-yl) piperazine was prepared by reported procedure, in brief synthesis began by 5-methyl-2-phenyl-2,4-dihydro-3H-pyrazol-3-one. Initially, performed the reaction of 5-methyl-2-phenyl-2,4-dihydro-3H-pyrazol-3-one with $POCl_3$ to afforded the 5-chloro-3-methyl-1-phenyl-1H-pyrazole 2 in 82% yield which in turn reacted with 1-Boc piperizene to afford the corresponding tert-butyl 4-(3-methyl-1-phenyl-1H-pyrazol-5-yl) piperazine-1-carboxylate 3. Compound 3 was reacting with MeOH. HCl to offered scaffold 4. 1-(3-methyl-1-phenyl-1H-pyrazol-5-yl) piperazine hydrochloride with various commercially available acids as depicted in Table 1.

The synthetic route is outlined in Scheme 1. 1-(3-methyl-1-phenyl-1H-pyrazol-5-yl) piperazine. HCl derivatives were synthesized from 5-methyl-2-phenyl-2,4-dihydro-3H-pyrazol-3-one. Initially,

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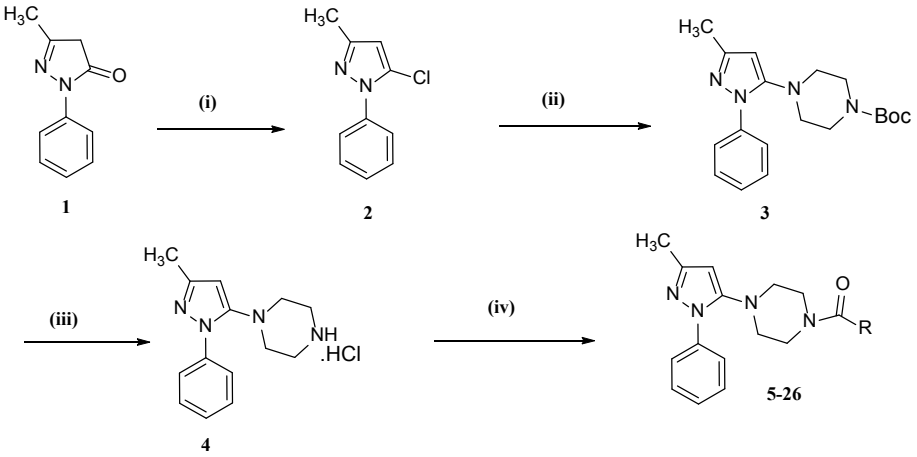

Scheme 1: Synthesis of amide derivatives, Reagents and conditions: (i) $POCl_3$, 80°C, 6 h: (ii) Boc-piperzene, K_2CO_3, DMA, Reflux, 5 h; (iii) MeOH.HCl, 0-RT, 2 h (iv) HATU, DIPEA, DCM, 8 h, RT, N_2.

Compd	CLogPa	MIC (μM)	Compd	CLogPa	MIC (μM)
5	4.46	25	16	3.13	25
6	4.54	>25	17	3.97	>25
7	3.6	>25	18	2.25	>25
8	3.23	>25	19	3.26	>25
9	4.37	10.5	20	8.12	25
10	4.37	12.5	21	3.31	>25
11	3.57	>25	22	2.35	>25
12	4.76	8.5	23	3.24	25
13	1.74	>25	24	4	>25
14	5.25	>25	25	3.76	12.5
15	4.18	25	26	2.77	>25
Isoniazid					0.66
Ethambutol					7.63
Ciprofloxacin					9.14

Table 1: Anti-mycobacterial activity of 7a-n and 8a-d against *Mycobacterium smegmatis*.

performed the reaction of 5-methyl-2-phenyl-2,4-dihydro-3H-pyrazol-3-one with $POCl_3$ to afforded the 5-chloro-3-methyl-1-phenyl-1H-pyrazole 2 in 82% yield which in turn reacted with 1-Boc piperizene to afford the corresponding tert-butyl 4-(3-methyl-1-phenyl-1H-pyrazol-5-yl)piperazine-1-carboxylate 3. Compound 3 was reacting with MeOH. HCl to offered scaffold 4. The coupling reactions of 4 with different acid afford amides 5-26 in excellent yields (Scheme 1). All the newly synthesized compounds 5-26 are well characterized by spectral data and then subjected to find their anti-mycobacterial activity studies.

In vitro anti-mycobacterial activity

All the synthesized compounds were screened against their in vitro anti-mycobacterial activity against M. tuberculosis H37Rv (MTB) by agar dilution method recommended by National Committee for Clinical Laboratory Standards for the determination of MIC and the values of the synthesized compounds along with standard drugs Isoniazid, Ethambutol and Ciprofloxacin for comparison are explained. Based on MIC values we could observe structure-activity relationship by the influence of substituted amides and urea derivatives. Anti-mycobacterial screening of 5-26 reveals that all the tested compounds showed moderate to good activity against the tested anti-mycobacterial assay and MIC's ranging from 9 to >25 g/mL. The compound 9 showed excellent activity against anti-mycobacteria. The compounds 5-8, 11 and 13-25 showed poor anti-mycobacterial activity. The activity of the 3-CF3 compound 9 and 3,4dichloro compound 12 potent against both replicating and non-replicating M. tuberculosis. When the 3-CF3 in the compound 9 was replace with 2-OMe group of compound 16 with a MIC of >25, was 4-fold less active. All experiments were carried out in triplicates and the results were reported as ± SD. From the anti-mycobacterial activity, the MIC values are calculated and presented. The values presented suggested that electronic effect may play a role in the anti-tuberculosis activity in this series.

Experimental Procedure

General information

Melting points reported in this work were recorded in capillary tubes on an Elchem lab melting point apparatus and uncorrected. ^1H and ^{13}C NMR were recorded on Bruker FT-NMR spectrometer either 300 MHz or 400 MHz using 5 mm PABBO BB-1H tubes. ^1HNMR spectra were recorded using approximately 0.03 M solutions in $CDCl_3$ with TMS as an internal reference. ^{13}C NMR spectra were recorded using approximately 0.05 M solutions in $CDCl_3$ at 100 MHz or 125 MHz. Chemical shift values were reported in parts per million (δ ppm) from internal standard TMS. UV-visible spectra were recorded on SYSTRONIC AU-2701 UV-Vis spectrophotometer. All reagents were purchased from Aldrich and used as received. Solvents were removed under reduced pressure on a rotavapour. Organic extracts were dried over anhydrous Na_2SO_4. Silica gel $60F_{254}$ coated aluminum sheets were used for TLC and silica gel (230400 meshes) was used for column chromatography. Visualization of spots on TLC plates was effected by UV illumination, exposure to iodine vapor and heating the plates dipped in $KMnO_4$ stain (Supplementary Figures 1-5).

Procedure for the synthesis of 5chloro3methyl1phenyl1H-pyrazole (2)

To a stirred solution of 5methyl2phenyl2,4dihydro3Hpyrazol3one 1 (1.0 mmol), Phosphorus oxychloride (5 ml) and heated for 6 hr at 80°C. The reaction mixture distills out u/vacuum. Add water and adjust the PH to 7.5 with sod. Carbonate extract the compound with ethyl acetate (2*75 ml), dried over Na_2SO_4 and the solvent were evaporated under reduced pressure. To get compound 2 (85% yield). ^1H NMR (300

MHz, DMSO) δ 7.64 (m, 3H), 7.53 (s, 2H), 6.84 (s, 1H), 2.75 (s, 3H); ^{13}C NMR (300 MHz, DMSO) δ 150.8, 138.4, 131.2, 130.8, 126.6, 125.6, 107.4, 14.5; MS: *m/z* 193.4 (*M* +H$^+$) (Supplementary Figures 6-12).

Procedure for the synthesis of tertbutyl 4(3methyl1phenyl-1Hpyrazol5yl) piperazine1carboxylate (3)

To a stirred solution of compound 2 (1 mmol) in DMA (50 ml) at RT. Add K_2CO_3 and bocpipererzene simultaneously. Stir the RM for 5 hr at reflux, monitor reaction by TLC. Distill out the solvent and water/ethyl acetate. Dried the organic layer with Na_2SO_4 and the solvent were evaporated under reduced pressure. To purify through column chromatography to get the **3** (80% yield). ^{1}H NMR (300 MHz, DMSO) δ 7.83 (d, 2H), 7.52 (t, 2H), 7.35 (t, 1H), 5.91 (s, 1H), 3.45 (m, 4H), 2.81 (m, 4H), 2.23 (s, 3H), 1.30 (s, 9H); ^{13}C NMR (300 MHz, DMSO) δ 158.2, 149.0, 139.1, 130.1, 126.9, 124.6, 90.8, 80.4, 52.3, 49.0, 30.2, 14.6; MS: *m/z* 343.6 (*M*+H$^+$) (Supplementary Figures 13-20).

Procedure for the synthesis of 1(3methyl1phenyl1Hpyrazol5yl) piperazine hydrochloride (4)

To the solution of compound 3 (1 mmol) in Methanol (25 ml), add MeOH. HCl a cooling and stir for 2 hr at RT. Cool to 010°c and stir for 30 mins. Filter the compound U/N_2 atm. Dried the compound u/vacuum to get compound 4 as solid (94% yield). ^{1}H NMR (300 MHz, DMSO) δ 7.82 (d, 2H), 7.51 (t, 3H), 7.26 (m, 1H), 6.01 (s, 1H), 2.84 (m, 4H), 2.61 (m, 4H), 2.30 (s, 3H); ^{13}C NMR (300 MHz, DMSO) δ 154.1, 149.4, 138.7, 130.1, 125.3, 124.8, 92.4, 51.0, 47.6, 13.9; MS: *m/z* 243.7 (*M* +H$^+$) (Supplementary Figures 21-23).

General procedure for compound preparation of 526

To the solution of compound 4 in CH_2Cl_2, add DIPEA and HATU simultaneously under N_2 atm. Corresponding acid was added to RM and stirred for 8 hr at RT. To the RM excess of CH_2Cl_2 added and wash with $NaHCO_3$ solution and brine solution. Dried the DCM layer over the Na_2SO_4 and concentrated under reduced pressure. Compound was purified by column chromatography (Ethyl Acetate: Hexane, 2:8) to afford products of 526.

(2bromo5fluorophenyl) (4(3methyl1phenyl1Hpyrazol5yl) piperazin1yl) methadone (5): Off white solid, 91% yield; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.73 (d, J=7.8 Hz, 2H), 7.52 (m, 1H), 7.41 (t, 2H), 7.28 (m, 1H), 6.98 (m, 2H), 5.71 (s, 1H), 3.85 (m, 2H), 3.25 (m, 2H), 2.94 (m, 3H), 2.78 (m, 2H), 2.27 (s, 3H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 166.3, 162.8, 160.8, 151.0, 148.9, 139.8, 139.1, 134.4, 134.4, 129.0, 126.6, 122.8, 117.9, 177.7, 115.2, 115.0, 94.5, 51.24, 50.5, 46.3, 41.2, 14.0; MS: *m/z* 443.0 (*M*+H$^+$), M. Formula: $C_{21}H_{20}BrFN_4O$.

2(2chlorophenyl)1(4(3methyl1phenyl1Hpyrazol5yl) piperazin1yl) ethan1one (6): Off white solid, 89% yield; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.74 (d, *J*=7.8 Hz, 2H), 7.40 (m, 3H), 7.23 (m, 4H), 5.67 (s, 1H), 3.80 (s, 2H), 3.70 (m, 2H), 3.48 (m, 2H), 2.86 (m, 2H), 2.75 (m, 2H), 2.26 (s, 3H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 168.6, 151.2, 148.9, 139.9, 133.7, 133.0, 130.5, 129.4, 128.9, 128.4, 127.0, 126.5, 122.7, 94.5, 51.1, 50.7, 45.5, 41.4, 37.8, 14.0; MS: *m/z* 395.1 (*M*+H$^+$), M. Formula: $C_{22}H_{23}ClN_4O$.

(2, 6dimethoxyphenyl) (4(3methyl1phenyl1Hpyrazol5yl) piperazin1yl) methanone (7): Off white solid, 93% yield; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.75 (d, J=7.5 Hz, 2H), 7.39 (t, 2H), 7.22 (m, 2H), 6.53 (d, J=8.4 Hz, 2H), 5.69 (s, 1H), 3.88 (m, 2H), 3.78 (s, 6H), 3.25 (m, 2H), 2.96 (m, 2H), 2.74 (m, 2H), 2.27 (s, 3H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 167.2, 156.7, 151.7, 149.0, 130.5, 129.1, 126.6, 122.8, 104.0, 94.4, 55.9, 51.6, 50.8, 46.2, 41.0, 14.2; MS: m/z 407.1 (*M*+H$^+$). M. Formula: $C_{23}H_{26}N_4O_3$.

(2hydroxyphenyl) (4(3methyl1phenyl1Hpyrazol5yl) piperazin1yl) methanone (8): Off white solid, 77% yield; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.51 (s, 1H), 7.75 (d, J=7.8 Hz, 2H), 7.42 (t, 2H), 7.31 (m, 2H), 7.20 (d, *J*=7.8 Hz, 1H), 6.99 (d, *J*=8.1 Hz, 1H), 6.83 (t, 1H), 5.71 (s, 2H), 3.76 (m, 4H), 2.92 (m, 4H), 2.28 (s, 3H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 170.9, 158.8, 151.1, 149.0, 139.8, 132.7, 129.0, 128.1, 126.6, 122.8, 118.6, 118.0, 116.8, 94.6, 51.1, 45.2, 14.0; MS: *m/z* 361.1 (*M*H$^+$), M. Formula: $C_{21}H_{22}N_4O_2$.

(4(3methyl1phenyl1Hpyrazol5yl)piperazin1yl)(3(trifluoromethyl) phenyl) methanone (9): Off white solid, 97% yield; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.74 (d, J=7.8 Hz, 2H), 7.67 (m, 2H), 7.54 (m, 2H), 7.41 (t, 2H), 7.24 (s, 1H), 5.71 (s, 1H), 3.84 (m, 2H), 3.42 (m, 2H), 2.97 (m, 2H), 2.81 (m, 2H), 2.28 (s, 3H); ^{13}C NMR (300 MHz, $CDCl^3$) δ 168.8, 151.0, 148.9, 139.8, 136.2, 131.2, 130.9, 130.2, 129.1, 128.9, 126.6, 124.8, 123.9, 122.8, 94.6, 50.9, 47.1, 41.7, 14.0; MS: *m/z* 415.3 (*M*+H$^+$), M. Formula: $C_{22}H_{21}F_3N_4O$.

(4(3methyl1phenyl1Hpyrazol5yl)piperazin1yl)(4(trifluoromethyl) phenyl) methanone (10): Off white solid, 93% yield; ^{1}H NMR 300 MHz, $CDCl_3$) δ 7.70 (m, 4H), 7.49 (d, *J*=7.8 Hz, 2H), 7.40 (t, 2H), 7.28 (m, 1H), 5.709 (s, 1H), 3.84 (m, 2H), 3.40 (m, 2H), 2.98 (m, 2H), 2.79 (m, 2H), 2.28 (s, 6H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 168.8, 151.0, 148.9, 139.8, 138.9, 131.8, 131.5, 128.9, 127.3, 126.5, 125.5, 124.9, 122.7, 122.1, 94.5, 51.1, 47.0, 41.6, 14.0; MS: *m/z* 415.1 (*M*+H$^+$), M. Formula: $C_{22}H_{21}F_3N_4O$.

(2fluorophenyl) (4(3methyl1phenyl1Hpyrazol5yl) piperazin1yl) methanone (11): Off white solid, 85% yield; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.74 (d, J=7.8 Hz, 2H), 7.39 (m, 4H), 7.24 (m, 2H), 7.07 (t, 1H), 5.70 (s, 1H), 3.86 (m, 2H), 3.34 (m, 2H), 2.91 (m, 2H), 2.80 (m, 2H), 2.27 (s, 3H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 165.3, 159.7, 156.4, 151.3, 149.0, 140.0, 131.5, 129.2, 126.7, 124.8, 123.9, 122.8, 116.0, 115.7, 94.6, 51.4, 50.8, 46.7, 41.6, 14.2; MS: *m/z* 364.9 (*M*+H$^+$), M. Formula: $C_{21}H_{21}FN_4O$.

(3, 4dichlorophenyl) (4(3methyl1phenyl1Hpyrazol5yl) piperazin1yl) methanone (12): Off white solid, 82% yield; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.73 (d, J= 7.8 Hz, 2H), 7.43 (m, 4H), 7.24 (m, 2H), 5.70 (s, 1H), 3.79 (m, 2H), 3.45 (m, 2H), 2.88 (m, 4H), 2.27 (s, 3H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 168.1, 151.1, 149.1, 139.9, 135.2, 134.4, 133.1, 130.8, 129.3, 129.1, 126.8, 126.4, 122.9, 94.7, 51.2, 47.3, 42.0, 14.2; MS: *m/z* 415.0 (*M*+H$^+$), M. Formula: $C_{21}H_{20}Cl_2N_4O$.

3(4(3methyl1phenyl1Hpyrazol5yl) piperazin1yl)3oxopropanenitrile (13): Off white solid, 95% yield; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.72 (d, *J*=7.8 Hz, 2H), 7.42 (t, 3H), 7.30 (m, 1H), 5.71 (s, 1H), 3.68 (s, 2H), 3.47 (m, 4H), 2.91 (m, 4H), 2.28 (s, 1H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 160.2, 150.8, 149.1, 139.9, 129.2, 126.9, 123.0, 94.8, 50.9, 50.6, 46.1, 42.2, 24.9, 14.2; MS: *m/z* 308.3 (*M*+H$^+$), M. Formula: $C_{17}H_{19}N_5O$.

2(2, 4dichlorophenyl)1(4(3methyl1phenyl1Hpyrazol5yl) piperazin1yl) ethan1one (14): Off white solid, 78% yield; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.74 (d, *J*=7.8 Hz, 2H), 7.41 (m, 3H), 7.25 (m, 3H), 5.68 (s, 1H), 3.74 (s, 2H), 3.69 (m, 2H), 3.50 (m, 2H), 2.83 (m, 4H), 2.27 (s, 3H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 168.2, 151.2, 149.0, 140.0, 134.3, 133.6, 131.8, 131.7, 129.3, 129.1, 127.4, 126.7, 122.8, 94.6, 51.3, 50.8, 45.5, 41.5, 37.2, 14.1; MS: *m/z* 429.1 (*M*+H$^+$), M. Formula: $C_{22}H_{22}Cl_2N_4O$.

1(4(3methyl1phenyl1Hpyrazol5yl) piperazin1yl)2(2,4,5trifluorophenyl) ethan1one (15): Off white solid, 89% yield; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.74 (d, *J*=7.8 Hz, 2H), 7.42 (t, 2H), 7.27 (m, 1H), 7.13 (m, 1H), 6.91 (m, 1H), 5.69 (s, 1H), 3.68 (m, 2H), 3.62 (s, 2H), 3.52 (m, 2H), 2.84 (m, 2H), 2.27 (s, 3H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 167.8,

151.2, 149.0, 140.0, 129.1, 126.7, 122.9, 119.1, 119.0, 118.8, 118.8, 105.7, 105.5, 105.4, 105.1, 94.7, 51.2, 50.8, 45.5, 41.6, 32.5, 14.1; MS: *m/z* 415.2 (*M*+H$^+$), M. Formula: $C_{22}H_{21}F_3N_4O$.

1(4(3methyl1phenyl1Hpyrazol5yl) piperazin1yl)2(3,4,5trimeth oxyphenyl)ethan1one (16): Off white solid, 81% yield; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.73 (d, *J*=7.8 Hz, 2H), 7.40 (t, 2H), 7.24 (m, 1H), 6.42 (s, 2H), 5.64 (s, 1H), 3.82 (s, 9H), 3.67 (m, 4H), 3.46 (s, 2H), 2.84 (m, 2H), 2.70 (s, 2H), 2.26 (s, 3H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 169.5, 153.5, 151.3, 149.1, 140.0, 137.0, 130.4, 129.1, 126.7, 122.8, 105.6, 94.6, 60.9, 56.2, 51.2, 50.9, 45.7, 41.4, 41.2, 14.1; MS: *m/z* 451.2 (*M*+H$^+$), M. Formula: $C_{25}H_{30}N_4O_4$.

2(4fluorophenyl)1(4(3methyl1phenyl1Hpyrazol5yl) piperazin1yl) ethan1one (17): Off white solid, 93% yield; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.72 (d, 2H), 7.40 (m, 2H), 7.23 (m, 3H), 7.01 (m, 2H), 5.65 (s, 1H), 3.67 (m, 4H), 3.45 (s, 2H), 2.83 (m, 2H), 2.673 (m, 2H), 2.26 (s, 3H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 169.3, 162.7, 160.7, 151.1, 148.9, 139.8, 130.3, 130.1, 130.0, 128.9, 126.5, 122.7, 115.6, 115.4, 94.4, 51.0, 50.6, 45.5, 41.3, 39.8, 14.0; MS: *m/z* 379.1 (*M*+H$^+$), M. Formula: $C_{22}H_{23}FN_4O$.

(4(3methyl1phenyl1Hpyrazol5yl) piperazin1yl) (pyridin4yl) methanone (18): Pale yellow solid, 79% yield; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.68 (d, *J*=5.7 Hz, 2H), 7.73 (d, *J*=7.8 Hz, 2H), 7.4 (t, 2H), 7.26 (m, 3H), 5.71 (s, 1H), 3.83 (m, 2H), 3.38 (m, 2H), 2.98 (m, 2H), 2.79 (m, 2H), 2.28 (s, 3H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 167.8, 151.0, 150.4, 149.0, 143.0, 139.9, 129.1, 126.7, 122.9, 121.1, 94.7, 51.4, 50.7, 47.0, 41.6, 14.1; MS: *m/z* 348.3 (*M*+H$^+$), M. Formula: $C_{20}H_{21}N_5O$.

(4(3methyl1phenyl1Hpyrazol5yl) piperazin1yl) (4nitrophenyl) methanone (19): Off white solid, 94% yield; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.27 (d, *J*=8.7 Hz, 2H), 7.73 (d, *J* = 7.8 Hz, 2H), 7.55 (d, J=8.4 Hz, 2H), 7.41 (t, 2H), 7.24 (m, 1H), 5.71 (s, 2H), 3.85 (m, 2H), 3.39 (m, 2H), 2.99 (m, 2H), 2.80 (m, 2H), 2.28 (s, 3H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 168.0, 150.9, 149.0, 148.4, 141.5, 139.8, 129.0, 128.0, 126.7, 123.9, 122.8, 94.6, 51.3, 50.7, 47.1, 41.8, 14.0; MS: *m/z* 390.1 (*M*H$^+$), M. Formula: $C_{21}H_{21}N_5O_3$.

1(4(3methyl1phenyl1Hpyrazol5yl) piperazin1yl) tetradecan1one (20): Off white solid, 88% yield; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.75 (d, J=7.8 Hz, 2H), 7.41 (t, 2H), 7.24 (m, 1H), 5.68 (s, 1H), 3.65 (m, 2H), 3.47 (m, 2H), 2.84 (m, 4H), 2.29 (m, 4H), 1.58 (m, 2H), 1.24 (m, 20H), 0.87 (t, 3H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 171.8, 151.3, 148.9, 139.9, 128.9, 126.5, 122.8, 94.4, 51.3, 50.8, 45.2, 41.0, 33.3, 31.8, 29.6, 29.5, 29.4, 29.4, 29.3, 29.3, 25.2, 22.6, 14.0; MS: *m/z* 453.2 (*M*+H$^+$), M. Formula: $C_{28}H_{44}N_4O$.

Tertbutyl 4(4(3methyl1phenyl1Hpyrazol5yl) piperazine1carbonyl) piperidine1carboxylate (21): Off white solid, 90% yield; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.75 (d, J= 7.5 Hz, 2H), 7.42 (t, 2H), 7.29 (m, 1H), 5.69 (s, 1H), 4.13 (m, 2H), 3.66 (m, 2H), 3.52 (m, 2H), 2.85 (m, 4H), 2.72 (m, 2H), 2.58 (m, 1H), 2.27 (s, 1H), 1.69 (m, 3H), 1.45 (S, 9H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 173.1, 154.7, 151.3, 149.0, 140.0, 129.1, 126.7, 122.9, 94.6, 79.7, 51.5, 50.9, 45.1, 43.3, 41.3, 38.5, 28.5, 28.4, 14.1; MS: *m/z* 453.2 (*M*+H$^+$), M. Formula: $C_{25}H_{35}N_5O_3$.

Cyclopropyl (4(3methyl1phenyl1Hpyrazol5yl) piperazin1yl) methanone (22): Off white solid, 84% yield; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.77 (d, J=7.5 Hz, 2H), 7.42 (t, 2H), 7.29 (m, 1H), 5.69 (s, 1H), 3.68 (m, 4H), 2.87 (m, 4H), 2.27 (s, 3H), 1.68 (m, 1H), 0.98 (m, 2H), 0.75 (m, 2H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 172.1, 151.4, 148.9, 139.9, 128.9, 126.5, 122.7, 94.4, 51.3, 50.7, 45.0, 41.6, 14.0, 10.9, 7.4; MS: *m/z* 311.1 (*M*+H$^+$), M. Formula: $C_{18}H_{22}N_4O$.

Cyclopentyl (4(3methyl1phenyl1Hpyrazol5yl) piperazin1yl) methanone (23): Off white solid, 96% yield; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.76 (d, J= 7.5 Hz, 2H), 7.41 (t, 2H), 7.27 (m, 1H), 5.68 (m, 1H), 3.66 (m, 2H), 3.53 (m, 2H), 2.84 (m, 4H), 2.27 (s, 3H), 1.76 (m, 7H), 1.55 (m, 2H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 174.5, 151.3, 148.8, 139.9, 128.8, 126.4, 122.7, 94.3, 51.3, 50.8, 44.9, 41.2, 40.9, 29.9, 25.8, 13.9; MS: *m/z* 339.3 (*M*+H$^+$), M. Formula: $C_{20}H_{26}N_4O$.

(2chloro5nitrophenyl) (4(3methyl1phenyl1Hpyrazol5yl) piperazin1yl) methanone (24): Off white solid, 92% yield; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.20 (m, 2H), 7.72 (d, J= 7.8 Hz, 2H), 7.58 (d, J=7.2 Hz, 1H), 7.41 (t, 2H), 7.28 (m, 1H), 5.72 (s, 1H), 3.88 (m, 2H), 3.27 (m, 2H), 3.01 (m, 2H), 2.83 (m, 2H), 2.28 (s, 3H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 164.6, 151.0, 149.1, 146.8, 139.9, 137.3, 136.8, 131.0, 129.2, 126.9, 125.1, 123.3, 123.0, 94.8, 51.4, 50.7, 46.5, 41.6, 14.2; MS: *m/z* 425.9 (*M*+H$^+$), M. Formula: $C_{21}H_{20}ClN_5O_3$.

(4(3methyl1phenyl1Hpyrazol5yl) piperazin1yl) (2methyl4nitrophenyl) methanone (25): Yellow solid, 75% yield; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.07 (m, 2H), 7.71 (d, J= 7.2 Hz, 2H), 7.40 (t, 2H), 7.30 (m, 2H), 5.71 (s, 1H), 3.88 (m, 2H), 3.21 (m, 2H), 2.99 (m, 2H), 2.76 (m, 2H), 2.41 (s, 3H), 2.27 (s, 3H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 167.9, 151.0, 149.1, 148.0, 142.0, 139.9, 136.6, 129.1, 127.0, 126.8, 125.5, 122.9, 121.4, 94.7, 51.5, 50.9, 46.4, 41.2, 19.2, 14.2; MS: *m/z* 406.1 (*M*+H$^+$), M. Formula: $C_{22}H_{23}N_5O_3$.

2(4(4(3methyl1phenyl1Hpyrazol5yl) piperazine1carbonyl) phenyl) acetonitrile (26): Off white solid, 83% yield; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.73 (d, *J*=7.8 Hz, 2H), 7.40 (m, 6H), 7.25 (m, 1H), 5.70 (s, 1H), 3.79 (m, 4H), 3.43 (s, 2H), 2.88 (m, 4H), 2.27 (s, 3H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 169.7, 151.2, 149.1, 139.9, 135.4, 131.8, 130.5, 129.1, 128.2, 127.9, 126.7, 117.3, 94.6, 51.2, 47.4, 41.9, 36.7, 23.9, 14.1; MS: *m/z* 386.3 (*M*+H$^+$), M. Formula: $C_{23}H_{23}N_5O$.

Conclusion

Highly substituted pyrazoles were synthesized from the corresponding starting material using HATU reagent. Biologically interesting heterocycles are produced in high yields. All the synthesized compounds are tested against anti-mycobacterial activity. Among them, 9, 10, 12 and 25 are identified as lead molecules. In particular, 9, and 12 are found to display promising activity.

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