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Synthesis Some Novel Pyrazolo[3,4-*D*]Pyrimidine Clubbed With Phenothiazine Nucleus and Their Biological Evaluation

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ABSTRACT

The reaction of 2-(methylthio)-10H-phenothiazine (**1**) with hydrazine hydrate afforded 1-(10H-phenothiazin-8-yl)hydrazine **(2)** and that with ethyl acetoacetate afforded 3-methyl-1-(10H-phenothiazin-8-yl)-1H-pyrazol-5(4H)-one **(3)**, which was condensed with different aromatic aldehydes and thiourea to give a series of 4,5-dihydro-4-(aryl)-3-methyl-1-(10H-phenothiazin-8-yl)-1H-pyrazolo[3,4-d]pyrimidine-6-thiols **(4a-h)**. The compounds **4a-h** were characterized by FT-IR, ^{1}H NMR, ^{13}C NMR, mass spectra and elemental analysis. All the newly synthesized compounds **4a-h** were evaluated for their antitubercular activity against Mycobacterium tuberculosis H_{37}Rv using radiometric BACTEC and broth dilution assay methods. The results show that compounds **4b**, **4d** and **4f** exhibited excellent anti-tubercular activity with percentage inhibition of 93, 91 and 96, respectively, at a MIC of <6.25 µg/mL. While, compounds **4a**, **4c**, **4e, 4g** and **4h** exhibited moderate to good anti-tubercular activity with percentage inhibition of 75, 68, 74, 54 and 63, respectively at a MIC of >6.25 µg/mL.

Keywords : Pyrazolopyrimidines, Phenothiazines, Antitubercular Activity, BACTEC Assay

I. INTRODUCTION

Nowadays, microorganisms resistant to multiple antimicrobial agents are a serious problem worldwide in the fight against infectious diseases, increasing morbidity and mortality with an overall increase in healthcare costs. In this context, Tuberculosis (TB) has become again an important public health problem worldwide since the mid-1980s, due to two major factors, the AIDS epidemic and the advent of multidrug resistant strains (MDR). TB is responsible for 20% of all deaths in adults, and each year there are about 8.9–9 millions of new cases, of which 15% are children, and 1.7–2 millions of deaths, of which 450,000 are children. Globally, the number of TB cases is currently rising at 2% per year with the estimative of 32% of the world population, about 2 billion people, being infected by latent TB. In the case of patients with AIDS, TB is the most common opportunistic infection and cause of death killing 1 of every 3 patients.[1] Due to the increase of MDR-TB and AIDS cases worldwide and the lack of new drugs nowadays, there is an urgent need for new drugs to fight against this disease.

In this context, Pyrazole and pyrimidine derivatives attracted organic chemists very much due to their biological and chemotherapeutic importance. Pyrazolopyrimidines and related fused heterocycles are of interest as potential bioactive molecules. They are known to exhibit pharmacological activities such as CNS depressant,[2] neuroleptic,[3] and tuberculostatic.[4] Pyrazolo[3,4-d]pyrimidines were identified as a general class of adenosine receptors.[5], [6] There is not much difference in the basic structures of pyrazolopyrimidines and purines. In the literature,

we have found that the replacement of 1H of pyrazole of pyrazolo[3,4-d]pyrimidine ring system by some other bioactive moiety drastically alters its pharmacological properties. Keeping this in mind, we have contemplated on the synthesis of pyrazolo[3,4-d]pyrimidine derivatives bearing a phenothiazine moiety.

Moreover, Phenothiazines have proven to be a pharmaceutically important class of heterocyles,[7] and due to their pharmacological efficacy they are applied as sedative, tranquilizers, anti-epilectic, antituberculer, bactericides and paraticides.[8] Interestingly, phenothiazines are able to cleave DNA upon photochemical induction.[9] Fairly early, it was recognized that due to the low oxidation potential of this class of tricyclic nitrogen-sulfur heterocycles, their propensity to form stable radical-cations play a key role in their physiological activities.[10] More recently, due to their reversible oxidation[11] phenothiazine derivatives have become attractive supramoleculer[12] and material scientific[13] motifs.

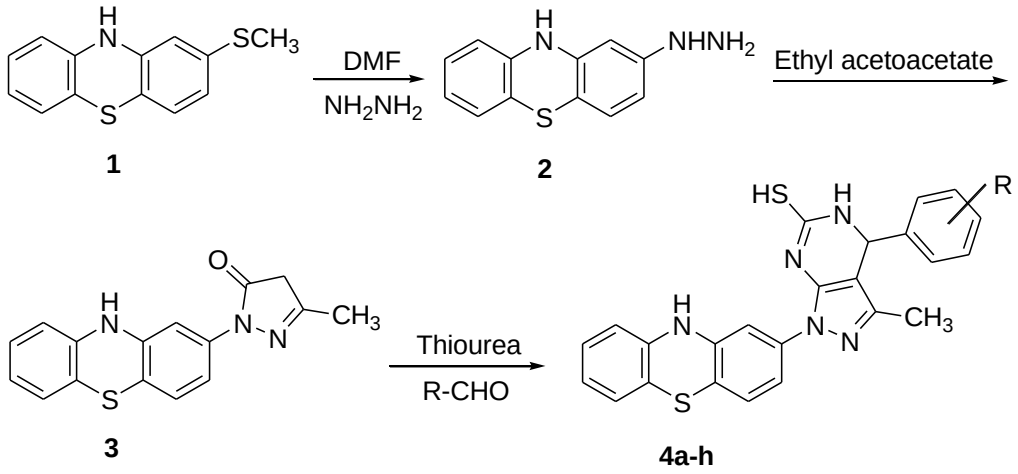
Keeping in mind the biomedical applications, as a continuation of our previous work[14], [15] and with a view to further assess the pharmacological profile of this class of compounds, we envisioned our approach toward the synthesis of a novel series of pyrazolo[3,4-d]pyrimidine derivatives by incorporating the phenothiazine and pyrazolo[3,4-d]pyrimidine in a single molecular framework with a potential spectrum of bio-responses. The anti-tubercular activities of the newly synthesized compounds against Mycobacterium tuberculosis $H_{37}Rv$ strain were studied using radiometric BACTEC and broth dilution assay methods.

II. CHEMISTRY

Classical Biginelli reaction was reported in 1893. Some of the drawbacks of Classical Biginelli eaction are that it requires high acidic condition, very long reaction time and poor yield of product. In last decades, research work on synthesis of Biginelli compounds has been generally increased due to their high pharmacological activity.

In order to promote conditions that would favor higher yields of products, we have recently performed Biginelli condensation using different catalyst such as PPA, $AlCl_3$, BF_3 etc. In this way, we have found that using phosphorus pentoxide as a catalyst in Biginelli's one-pot protocol, a significant increase in the yields of DHPMs was observed, especially for systems that give only moderate yields using traditional Biginelli conditions.

Different pyrimidine derivatives containing a phenothiazine nucleus were synthesized under reflux temperature. Reaction of 3-methyl-1-(10H-phenothiazin-8-yl)-1H-pyrazol-5(4H)-one **(3)**, an appropriate aldehyde and thiourea in the presence of catalytic amount of phosphorus pentoxide under reflux condition afforded 4,5-dihydro-4-(aryl)-3-methyl-1-(10H-phenothiazin-8-yl)-1H-pyrazolo[3,4-d]pyrimidine-6-thiols **(4a-h)**. The yields of the products were found to be excellent (80-90%). The structures of the synthesized compounds were assigned on the basis of IR, ^{1}H NMR spectra, ^{13}C NMR, mass spectra and purity was proven by elemental analysis. In ^{1}H NMR spectra of **(4a-h)** a sharp peak representing methine proton of pyrimidine is observed in the range of 4.88-4.97 δppm confirms the formation of pyrazolo[3,4-d]pyrimidine nucleus.



Figuer 1

III. BIOLOGICAL ACTIVITY

In vitro evaluation of the anti-tubercular activity was carried out at the Tuberculosis Acquisition Antimicrobial Coordinating Facility (TAACF) screening program, Alabama, USA. Minimum Inhibitory Concentration (MIC) was determined against Mycobacterium tuberculosis $H_{37}Rv$ by using the radiometric BACTEC[16], [17] and broth dilution[18], [19] assay methods, respectively. The result of anti-tubercular activity is presented in Table 1.

Table 1. In vitro antitubercular screening data of **4a-h**

Compound.	R	Molecular Formula	MIC μg/mL	% Inhibition
4a	Phenyl	$C_{24}H_{19}N_5S_2$	>6.25	75
4b	2-Hydroxyphenyl	$C_{24}H_{19}N_5OS_2$	<6.25	93
4c	4-Hydroxyphenyl	$C_{24}H_{19}N_5OS_2$	>6.25	68
4d	2-Chlorophenyl	$C_{24}H_{18}N_5S_2Cl$	<6.25	91
4e	4-Chlorophenyl	$C_{24}H_{18}N_5S_2Cl$	>6.25	74
4f	2-Nitrophenyl	$C_{24}H_{18}N_6O_2S_2$	<6.25	96
4g	4-Nitrophenyl	$C_{24}H_{18}N_6O_2S_2$	>6.25	54
4h	4-Methoxyphenyl	$C_{25}H_{21}N_5OS_2$	>6.25	63

The activity is considerably affected by substitutions at the phenyl ring of the pyrazolo[3,4-d]pyrimidine nucleus. It has been observed that compounds **4b**, **4d** and **4f** having methoxy, chloro and nitro group at 2nd position, showed excellent anti-tubercular activity with percentage inhibition of 93, 91 and 96, respectively, at a MIC of <6.25 μg/mL. While, presence of same substituents at any other position of phenyl ring remarkably reduced the anti-tubercular activity.

IV. CONCLUSION

In the present paper, we report the synthesis, spectral studies and anti-tuberculosis activity of a novel series pyrazolo[3,4-d]pyrimidine containing phenothiazine nucleus. The preliminary in vitro anti-tuberculosis screening of these novel series of 4,5-dihydro-4-(aryl)-3-methyl-1-(10H-phenothiazin-8-yl)-1H-pyrazolo[3,4-d]pyrimidine-6-thiols has evidenced that substitutions at 2nd position on the phenyl ring of

the pyrazolo[3,4-d]pyrimidine nucleus, have emerged as potential compounds endowed with excellent anti-tuberculosis activity. On the contrary, substituents at any other position of phenyl ring showed remarkable decrease in the anti-tuberculosis activity. The possible decrease of anti-tuberculosis activity of this basic pyrazolo[3,4-d]pyrimidine structure through modulation of ring substituents and warrants further investigations. In summary, we have identified a novel series of pyrazolo[3,4-d]pyrimidine containing phenothiazine nucleus, which may develop into the potential class of anti-tubercular agents.

V. EXPERIMENTAL

4.1. Materials and Methods

Melting points were determined in open capillary tubes and are uncorrected. Formation of the compounds was routinely checked by TLC on silica gel-G plates of 0.5 mm thickness and spots were located by iodine. ^{1}H NMR was determined in $CDCl_3$ solution on a Bruker DPX 300 MHz spectrometer. ^{13}C-NMR (75 and 125 MHz) spectra were registered on a Bruker AC 200, DPX 300 and ARX 500, at 25 °C, in $CDCl_3$. IR spectra were recorded on Shimadzu 8400 spectrometer in KBr. Elemental analysis of the newly synthesized compounds was carried out on Carlo Erba 1108 analyzer and are found within the range of theoretical value.

4.2. 1-(10H-phenothiazin-8-yl)hydrazine (2).

A mixture of 2-(methylthio)-10H-phenothiazine (0.01 mol) and Hydrazine hydrate (10 mL) was refluxed for 8 hrs. on an oil bath. The reaction mixture was poured in to ice cold water and product was recrystallized from ethanol. Yield 82%, m.p. 122 ºC; IR (KBr, cm^{-1}): 3335 (NH), 653 (C-S-C). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.45-7.76 (m, 7H, Ar-H), 9.15 (s, 1H, NH), 7.86-7.95 (m, 3H, $NHNH_2$). ^{13}C NMR ($CDCl_3$) δ: 105, 105.6, 109, 113, 118.2, 124.1, 126.2, 129.4, 143, 144.3, 151.5; MS m/z (%): 229. Anal. Calcd. for $C_{12}H_{11}N_3S$: C, 62.86; H, 4.84; N, 18.33. Found: C, 62.72; H, 4.72; N, 18.26%.

4.3. Synthesis of 3-methyl-1-(10H-phenothiazin-8-yl)-1H-pyrazol-5(4H)-one (3).

A mixture of 1-(10H-phenothiazin-8-yl)hydrazine (2.29 g, 0.01 mol) and ethyl acetoacetate (1.3 mL, 0.01 mol) in sodium ethoxide (20 mL) was heated under refluxed condition for 12 hours. The reaction mixture was poured into ice cold water and product was recrystallized from ethanol. Yield 68%, m.p. 113 ºC; IR (KBr, cm^{-1}): 3330 (NH), 650 (C-S-C). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 2.47 (s, 3H, CH_3), 4.26 (s, 2H, CH_2), 7.66-7.90 (m, 7H, Ar-H), 9.03 (s, 1H, NH). ^{13}C NMR ($CDCl_3$) δ: 15.8, 41.1, 112.5, 112.9, 113.2, 115, 117.1, 121.7, 128.2, 129.3, 137.8, 142.3, 163.4, 175.6; MS m/z (%): 295. Anal. Calcd. for $C_{16}H_{13}N_3OS$: C, 65.06; H, 4.44; N, 14.23. Found: C, 64.92; H, 4.29; N, 14.31%.

4.4. General procedure for the synthesis 4,5-dihydro-4-(aryl)-3-methyl-1-(10H-phenothiazin-8-yl)-1H-pyrazolo[3,4-d]pyrimidine-6-thiols (4a-h)

An equimolar mixture of 3-methyl-1-(10H-phenothiazin-8-yl)-1H-pyrazol-5(4H)-one **(3)**, an appropriate aldehyde (0.01 mol) and thiourea (0.01 mol) was heated under refluxed in ethanol (30ml) in the presence of phosphorus pentoxide (200 mg) as a catalyst for 5 hours. Then the reaction mixture was kept at room temperature for 2 hours. The yellow crystalline products so obtained was isolated and recrystallized from ethanol.

4.4.1 4,5-dihydro-4-(phenyl)-3-methyl-1-(10H-phenothiazin-8-yl)-1H-pyrazolo [3,4-d]pyrimidine-6-thiol (4a)

Yield 72%, m.p. 121 ºC; IR (KBr, cm^{-1}): 3333, 1614, 1640, 650. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 2.40 (s, 3H, CH_3), 4.93 (s, 1H, CH), 7.37-7.53 (m, 12H, Ar-H), 8.38 (s, 1H, NH), 9.02 (s, 1H, NH). ^{13}C NMR ($CDCl_3$) δ: 25.8, 40.7, 50.2, 60.5, 101.8, 102.4, 105.2, 115.1, 116.3, 122.5, 126, 127.3, 127.9, 128.2, 128.8, 135.3, 142.5, 144.1, 155.8, 164.7; MS m/z (%): 441. Anal. Calcd. for $C_{24}H_{19}N_5S_2$: C, 65.28; H, 4.34; N, 15.86. Found: C, 65.15; H, 4.16; N, 15.74%.

4.4.2 4,5-dihydro-4-(2-hydroxyphenyl)-3-methyl-1-(10H-phenothiazin-8-yl)-1H -pyrazolo[3,4-d]pyrimidine-6-thiol (4b)

Yield 78%, m.p. 157 ºC; IR (KBr, cm^{-1}): 3330, 1610, 1642, 655. ^1H NMR (300 MHz, $CDCl_3$) δ: 2.42 (s, 3H, CH_3), 4.95 (s, 1H, CH), 7.48-7.72 (m, 11H, Ar-H), 8.40 (s, 1H, NH), 9.11 (s, 1H, NH), 10.08 (s, 1H, OH). ^{13}C NMR ($CDCl_3$) δ: 26.2, 34.1, 52.3, 60, 103, 103.6, 105.3, 114.2, 115.5, 116.3, 121.7, 122.6, 127.2, 127.5, 127.9, 128.6, 142.3, 143.8, 155.1, 155.8, 163.4; MS m/z (%):457. Anal. Calcd. for $C_{24}H_{19}N_5OS_2$: C, 63.00; H, 4.19; N, 15.31. Found: C, 62.91; H, 4.26; N, 15.21%.

4.4.3 4,5-dihydro-4-(4-hydroxyphenyl)-3-methyl-1-(10H-phenothiazin-8-yl)-1H -pyrazolo[3,4-d]pyrimidine-6-thiol (4c)

Yield 81%, m.p. 171 ºC; IR (KBr, cm^{-1}): 3328, 1612, 1642, 645. ^1H NMR (300 MHz, $CDCl_3$) δ: 2.44 (s, 3H, CH_3), 4.98 (s, 1H, CH), 7.13-8.10 (m, 11H, Ar-H), 8.35 (s, 1H, NH), 9.09 (s, 1H, NH), 10.15 (s, 1H, OH). ^{13}C NMR ($CDCl_3$) δ: 26.8, 41.5, 52.3, 59.3, 103.2, 103.8, 105.2, 114.4, 116, 122.3, 127.2, 127.5, 128, 128.4, 142.3, 143.1, 155.8, 156, 163.2; MS m/z (%): 457. Anal. Calcd. for $C_{24}H_{19}N_5OS_2$: C, 63.00; H, 4.19; N, 15.31. Found: C, 62.93; H, 4.25; N, 15.21%.

4.4.4 4,5-dihydro-4-(2-chlorophenyl)-3-methyl-1-(10H-phenothiazin-8-yl)-1H -pyrazolo[3,4-d]pyrimidine-6-thiol (4d)

Yield 76%, m.p. 164 ºC; IR (KBr, cm^{-1}): 3325, 1615, 1643, 648. ^1H NMR (300 MHz, $CDCl_3$) δ: 2.35 (s, 3H, CH_3), 4.88 (S, 1H, CH), 7.68-7.80 (m, 11H, Ar-H), 8.38 (s, 1H, NH), 9.13 (s, 1H, NH). ^{13}C NMR ($CDCl_3$) δ: 26.1, 36.2, 52, 60.3, 103.5, 103.8, 105, 114.3, 116.7, 122.1, 126.7, 127.5, 127.9, 128.2, 129, 129.5, 133.6, 139.2, 142.8, 143.5, 155.1, 162.4; MS m/z (%): 476. Anal. Calcd. for $C_{24}H_{18}N_5S_2Cl$: C, 60.56; H, 3.81; N, 14.71. Found: C, 60.49; H, 3.70; N, 14.62%.

4.4.5 4,5-dihydro-4-(4-chlorophenyl)-3-methyl-1-(10H-phenothiazin-8-yl)-1H -pyrazolo[3,4-d]pyrimidine-6-thiol (4e): Yield 79%, m.p. 144 ºC; IR (KBr, cm^{-1}): 3327, 1611, 1648, 650. ^1H NMR (300 MHz, $CDCl_3$) δ: 2.38 (s, 3H, CH_3), 4.90 (s, 1H, CH), 7.32-8.23 (m, 11H, Ar-H), 8.43 (s, 1H, NH), 9.05 (s, 1H, NH). ^{13}C NMR ($CDCl_3$) δ: 26, 41.2, 52.3, 59.6, 103.3, 104, 105.6, 114.7, 116.2, 122.3, 127.2, 127.9, 128, 128.5, 128.9, 132.1, 134.5, 142.3, 143.6, 155.7, 162.5; MS m/z (%): 476. Anal. Calcd. for $C_{24}H_{18}N_5S_2Cl$: C, 60.56; H, 3.81; N, 14.71. Found: C, 60.47; H, 3.87; N, 14.64%.

4.4.6 4,5-dihydro-4-(2-nitrophenyl)-3-methyl-1-(10H-phenothiazin-8-yl)-1H-pyrazolo[3,4-d]pyrimidine-6-thiol (4f)

Yield 83%, m.p. 232 ºC; IR (KBr, cm^{-1}): 3338, 1608, 1648, 658. ^1H NMR (300 MHz, $CDCl_3$) δ: 2.46 (s, 3H, CH_3), 4.94 (s, 1H, CH), 7.28-7.55 (m, 11H, Ar-H), 8.28 (s, 1H, NH), 9.21(s, 1H, NH). ^{13}C NMR ($CDCl_3$) δ: 26.5, 36.1, 51.1, 59.2, 103.1, 103.5, 105, 114.7, 116.7, 122.3, 124.8, 126.3, 127, 127.8, 128.1, 128.9, 134.3, 135.5, 142.7, 143.2, 148.5, 155.5, 163.3; MS m/z (%): 486. Anal. Calcd. for $C_{24}H_{18}N_6O_2S_2$: C, 59.24; H, 3.73; N, 17.27. Found: C, 59.15; H, 3.81; N, 17.18%.

4.4.7 4,5-dihydro-4-(4-nitrophenyl)-3-methyl-1-(10H-phenothiazin-8-yl)-1H -pyrazolo[3,4-d]pyrimidine-6-thiol (4g)

Yield 74%, m.p. 196 ºC; IR (KBr, cm^{-1}): 3335, 1610, 1650, 654. ^1H NMR (300 MHz, $CDCl_3$) δ: 2.33 (s, 3H, CH_3), 4.97 (S, 1H, CH), 7.76-7.93 (m, 11H, Ar-H), 8.32 (s, 1H, NH), 9.17 (s, 1H, NH). ^{13}C NMR ($CDCl_3$) δ: 26.3, 40.2, 52.5, 59.3, 103.1, 103.8, 105.2, 114.3, 116.3, 121.8, 122.5, 127.3, 127.8, 128.2, 129.9, 134.2, 140.5, 142.3, 143.8, 147.6, 155.4, 163.8; MS m/z (%): 486. Anal. Calcd. for $C_{24}H_{18}N_6O_2S_2$: C, 59.24; H, 3.73; N, 17.27. Found: C, 59.18; H, 3.60; N, 17.14%.

4.4.8 4,5-dihydro-4-(4-methoxyphenyl)-3-methyl-1-(10H-phenothiazin-8-yl)-1H -pyrazolo[3,4-d]pyrimidine-6-thiol (4h)

Yield 77%, m.p. 202 ºC; IR (KBr, cm^{-1}): 3332, 1613, 1654, 652. ^1H NMR (300 MHz, $CDCl_3$) δ: 2.37 (s, 3H, CH_3), 3.70 (s, 3H, OCH_3), 4.91 (s, 1H, CH), 7.31-7.98 (m, 11H, Ar-H), 8.30 (s, 1H, NH), 9.07 (s, 1H, NH). ^{13}C NMR ($CDCl_3$) δ: 26.5, 40.2, 52.4, 60.3, 103.2, 103.9, 104.9, 114.5, 116.5, 122.8, 126.1, 127.8, 128.6, 129.1, 133.3, 136, 142.3, 149.3, 155.9, 164.1; MS m/z (%):

471. Anal. Calcd. for $C_{25}H_{21}N_5OS_2$: C, 63.67; H, 4.49; N, 14.85. Found: C, 63.56; H, 4.52; N, 14.79%.

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