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MEDICINAL CHEMISTRY RESEARCH

ORIGINAL RESEARCH

Synthesis and anti-tubercular evaluation of some novel pyrazolo[3,4-*d*]pyrimidine derivatives

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Abstract A series of phenothiazine clubbed pyrazolo[3,4-*d*]pyrimidines have been synthesized by using the Biginelli multi-component cyclocondensation reaction and their ability to inhibit growth of *Mycobacterium tuberculosis* in vitro have been determined. 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 minimum inhibitory concentration (MIC) of <6.25 μg/ml, whereas 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.

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Introduction

Tuberculosis is an infectious pulmonary disease caused by the pathogen *Mycobacterium tuberculosis* that is responsible for infecting 8–10 million people globally and three million deaths every year according to a World Health Organization report. Owing to the rapid spread of tuberculosis strains resistant to all first-line anti-tubercular drugs such as isoniazid, rifamcin, and ethionamide, and due to the toxicity of second-line drugs, such as ethionamide, aminosalicylic acid, cycloserine, amikacin, kanamycin, and capreomycin, the discovery of new anti-tubercular agents with potential activity, less toxicity, broader spectrum, and safer therapeutic profiles, is an urgent need (Scior *et al.*, 2002; Tripathi *et al.*, 2005).

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 (Julino and Stevens, 1998; Ibrahim Abdou *et al.*, 2004), neuroleptic (Filler, 1974), and tuberculostatic (Ghorab *et al.*, 2004). Pyrazolo[3,4-*d*]pyrimidines were identified as a general class of adenosine receptors (Davies *et al.*, 1984). In the literature, we have found that the replacement of 1*H* 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 form an important class of heterocyclic compounds possessing wide spectrum diverse biological activities like sedative, tranquilizers, anti-epileptic, anti-tubercular, bactericides, and parasiticides (Mietzsch, 1954; Okafor, 1977; Albery *et al.*, 1979). Interestingly, phenothiazines are able to cleave DNA upon photochemical induction (Nishiwaki *et al.*, 1990). 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 (Moutet and Reverdy, 1983). More recently, owing to their reversible oxidation (Mcintyre and Gerischer, 1984), phenothiazine derivatives have become attractive supramolecular (Duesing *et al.*, 1990; Brun *et al.*, 1991) and material scientific motifs (Knorr and Daub, 1995; Spreitzer and Daub, 1996).

Keeping in mind the biomedical applications, as a continuation of our previous study (Trivedi *et al.*, 2008a, b) 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 *M. tuberculosis* $H_{37}Rv$ strain were studied using radiometric BACTEC and broth dilution assay methods.

Experimental

General

Melting points were determined in open capillary tubes and are uncorrected. Thin layer chromatography (TLC) was performed on Silica gel G (Merck) in the solvent system–ethyl acetate:hexane (3:7, v/v); iodine chamber was used for visualization of TLC spots. ^{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.

Chemistry

*Synthesis of 1-(10H-phenothiazin-8-yl)hydrazine (**2**)*

A mixture of 2-(methylthio)-10*H*-phenothiazine (0.01 mol) and hydrazine hydrate (10 ml) was refluxed for 8 h on an oil bath. The reaction mixture was poured into ice-cold water and product was recrystallized from ethanol. Yield 82%, mp 122°C, Rf-value 0.60; 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%.

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

A mixture of 1-(10*H*-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 h. The reaction mixture was poured into ice-cold water, and the product was recrystallized from ethanol. Yield 68%, mp 113°C, Rf-value 0.59; 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%.

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

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

Yield 72%, mp 121°C; Rf-value 0.66; 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, ^{1}H, 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%.

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

Yield 78%, mp 157°C; Rf-value 0.62; 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%.

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

Yield 81%, mp 171°C; Rf-value 0.55; 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%.

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

Yield 76%, mp 164°C; Rf-value 0.60; 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%.

4,5-Dihydro-4-(4-chlorophenyl)-3-methyl-1-(10H-phenothiazin-8-yl)-1H-pyrazolo[3,4-d]pyrimidine-6-thiol ***(4e)***

Yield 79%, mp 144°C; Rf-value 0.57; 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%.

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

Yield 83%, mp 232°C; Rf-value 0.63; 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%.

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

Yield 74%, mp 196°C; Rf-value 0.67; 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%.

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

Yield 77%, mp 202°C; Rf-value 0.58; 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%.

Results and discussion

Chemistry

Classical Biginelli reaction was reported in 1893. Some of the drawbacks of Classical Biginelli reaction are that it requires high acidic condition, very long reaction time, and

poor yield of product. In last decades, research work on the 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 catalysts 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-(10*H*-phenothiazin-8-yl)-1*H*-pyrazol-5(4*H*)-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-(10*H*-phenothiazin-8-yl)-1*H*-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, and 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 was observed in the range of 4.88–4.97 δppm confirming the formation of pyrazolo[3,4-*d*]pyrimidine nucleus (Scheme 1).

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 *M. tuberculosis* H_{37}Rv by using the radiometric BACTEC (Collins and Franzblau, 1997; Franzblau *et al.*, 1998) and broth dilution (Yajko *et al.*, 1995; Suling *et al.*, 2000) assay methods. The result of anti-tubercular activity is presented in Table 1.

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 second position, showed excellent anti-tubercular activity with percentage inhibition of 93, 91, and 96, respectively, at a MIC of <6.25 μg/ml, whereas the presence of same substituents at any other position of phenyl ring remarkably reduced the anti-tubercular activity.

Conclusions

In the present article, we report the synthesis, spectral studies, and anti-tuberculosis activity of a novel series pyrazolo [3,4-*d*]pyrimidine containing phenothiazine nucleus. The

Scheme 1 Reaction scheme

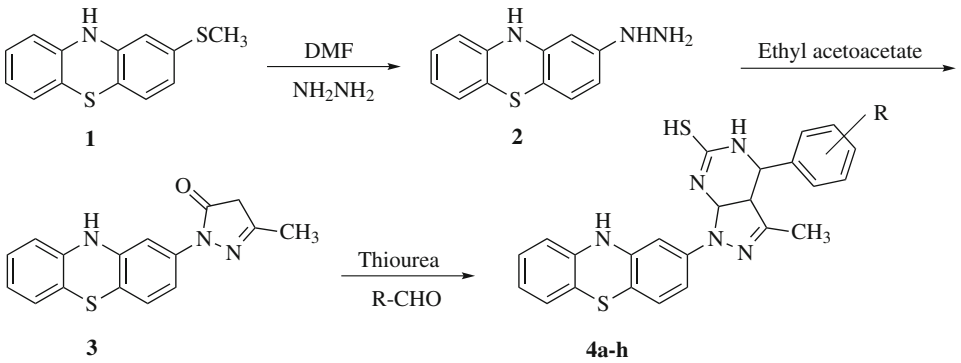

Table 1 In vitro antitubercular screening data of **4a–h**

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

preliminary in vitro anti-tuberculosis screening of these novel series of 4,5-dihydro-4-(aryl)-3-methyl-1-(10*H*-phenothiazin-8-yl)-1*H*-pyrazolo[3,4-*d*]pyrimidines 6-thiols has evidenced that substitutions at second 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 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.

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