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Original article

A facile four-component sequential protocol in the expedient synthesis of novel 2-aryl-5-methyl-2,3-dihydro-1*H*-3-pyrazolones in water and their antitubercular evaluation

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ABSTRACT

A series of 2-aryl-5-methyl-2,3-dihydro-1*H*-3-pyrazolones has been synthesized by one-pot, four-component sequential reactions of phenylhydrazine, methyl acetoacetate, aromatic aldehydes and β-naphthol in the presence of *p*-toluenesulphonic acid in water in good yields. These 2-aryl-5-methyl-2,3-dihydro-1*H*-3-pyrazolones were screened for *in-vitro* antimycobacterial activity against *Mycobacterium tuberculosis* H37Rv (MTB) using agar dilution method. Among the 15 compounds screened, 4-[(2,4-dichlorophenyl)(2-hydroxy-1-naphthyl)methyl]-2-(4-fluorophenyl)-5-methyl-2,3-dihydro-1*H*-3-pyrazolone displays the maximum potency with a minimum inhibitory concentration (MIC) of 1.6 μM against MTB, being 2.94 and 4.75 times more active than ciprofloxacin and ethambutol respectively.

1. Introduction

Pyrazolones have gained importance as drug substances in pharmaceutical industry in view of their biological importance. For instance, the pyrazolones, *viz.* phenazone, propyphenazone, ampyrone and metamizole (Fig. 1) are useful antipyretic and analgesic drugs [1], whilst edaravone (MCI-186) has been used for treating brain [2,3] and myocardial ischemia [4]. In addition, pyrazolones possess antimicrobial, antifungal [5], antimycobacterial [6,7], antibacterial [8], anti-inflammatory [9], antitumor [10], gastric secretion stimulatory [11], antidepressant [12] and antifilarial activities [13]. They also serve as precursors for dyes, pigments, pesticides and chelating agents [14], besides finding applications in the extraction and separation of various metal ions [15–19]. They are also employed in chromatography, petrochemical industry, as laser materials and ^{1}H NMR shift reagents [20–23].

Tuberculosis (TB) is a contagious disease caused by respiratory infection from the Gram positive bacterium, *Mycobacterium tuberculosis*, which in recent years has become an important worldwide public health problem with one-third of the world's population infected by the TB bacillus resulting in a death toll of 2 million [24]. According to World Health Organization, within the next 20 years, approximately 30 million people will be infected with the bacillus [25]. Further, the emergence of multi-drug-resistant TB (MDR-TB) that resists two or more of the first-line anti-TB drugs, *viz.* isoniazid, rifampicin, pyrizinamide, ethambutol, and streptomycin [26] and extensively drug-resistant tuberculosis (XDR-TB) further aggravates the problems associated with TB. The root of the drug resistance problem lies in the complexity and length of drug-sensitive treatment regimens. The pathogenic synergy of tuberculosis with HIV [27] also enhances the overall incidence of TB in HIV-positive patients by 50 times relative to the rate for HIV-negative individuals [28]. Furthermore, no new drugs were introduced during last few decades, except the recently introduced fluoroquinolones, which discloses the lack of significant research by pharmaceutical industry in this area. Consequently, the development of new affordable drugs with novel mechanisms of action and shorter and simpler regimens capable of effectively treating MDR- and XDR-TB is of great importance.

Literature survey reveals that pyrazoline derivatives are active against many mycobacteria [7,29]. The present work emerges as

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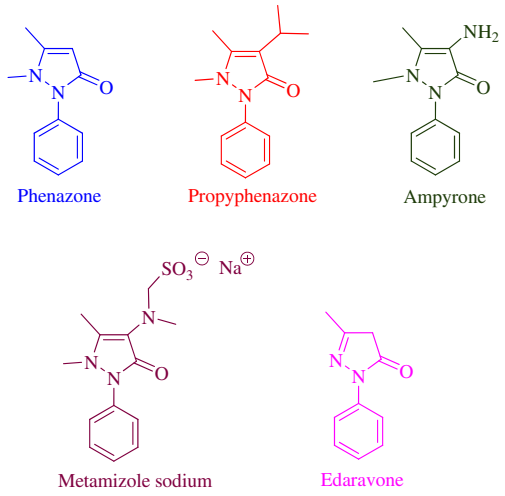
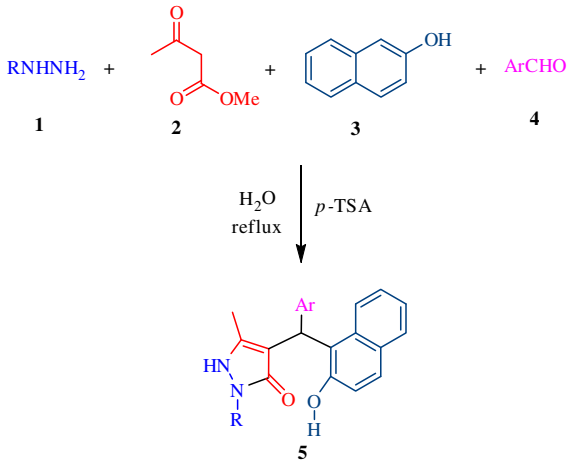


Fig. 1. Some pyrazolone drugs.



Scheme 1. Synthesis of 2-aryl-5-methyl-2,3-dihydro-1*H*-3-pyrazolones **5**.

a part of our research programme recently embarked on the synthesis of novel heterocycles employing tandem/domino reactions and/or their *in-vitro* screening for biological activities [30] and/or unearth new lead molecules with antimycobacterial activities [31]. Hence we have now synthesized novel 2-aryl-5-methyl-2,3-dihydro-1*H*-3-pyrazolones, screened them for preliminary *in-vitro* antitubercular activity against *M. tuberculosis* H37Rv (MTB) and present the results in this paper.

2. Chemistry

The biological importance of pyrazolones mentioned above prompted us to evolve an efficient, convergent, four-component sequential protocol for the synthesis of 2-aryl-5-methyl-2,3-dihydro-1*H*-3-pyrazolones **5** from the reaction of arylhydrazine **1**, methyl acetoacetate **2**, β-naphthol **3** and aromatic aldehydes **4a**–**i** in water in the presence of *p*-toluenesulphonic acid (*p*-TSA), a mild Bronsted acid. The choice of water as the medium in the present work is driven by the fact that it is the most abundant, cheapest, safest and the least toxic solvent, which enables the transformations green, besides the unique reactivity and selectivity

Table 1
Screening of catalysts, solvents and reaction conditions.

Entry	Catalyst	Solvent	Conditions	Reaction time (h)	Yield[a,b] (%)
1	–	H_2O	Reflux	20	–[c]
2	*p*-TSA	H_2O	Reflux	6	74
3	*p*-TSA	CH_3CN	Reflux	7	55
4	*p*-TSA	EtOH	Reflux	9	35
5	*p*-TSA	$CHCl_3$	Reflux	20	–[c]
6	*p*-TSA	Solvent-free	110 °C	5	40
7	–	Solvent-free	110 °C	20	–[c]
8	$InCl_3$	CH_3CN	Reflux	20	25
9	$InCl_3$	EtOH	Reflux	20	33
10	$InCl_3$	$CHCl_3$	Reflux	20	15
11	$InCl_3$	H_2O	Reflux	15	–[c]
12	$InCl_3$	Solvent-free	110 °C	18	40
13	K10 clay	CH_3CN	Reflux	7	48
14	K10 clay	EtOH	Reflux	7	39
15	K10 clay	$CHCl_3$	Reflux	20	26
16	K10 clay	H_2O	Reflux	20	–[c]
17	K10 clay	Solvent-free	110 °C	20	–[c]

[a] All reactions carried out with phenylhydrazine (1 mmol), methyl acetoacetate (1 mmol), 4-chlorobenzaldehyde (1 mmol), β-naphthol (1 mmol) and catalyst (10 mol%).
[b] Yield of isolated product.
[c] Reaction failed to occur.

Table 2
Synthesis of 2-aryl-5-methyl-2,3-dihydro-1*H*-3-pyrazolones **5** along with their MIC values.

Entry	Product	R	Ar	Reaction time (h)	Yield[a] (%)	MIC (μM)
1	**5a**	C_6H_5	4–$O_2NC_6H_4$	5	75	6.9
2	**5b**	C_6H_5	2–$O_2NC_6H_4$	4	72	13.8
3	**5c**	C_6H_5	4–ClC_6H_4	6	74	14.1
4	**5d**	C_6H_5	C_6H_5	8	62	30.8
5	**5e**	C_6H_5	4–$Pr^iC_6H_4$	7	59	14.0
6	**5f**	C_6H_5	4–$MeOC_6H_4$	6	63	28.6
7	**5g**	C_6H_5	4–MeC_6H_4	10	58	29.7
8	**5h**	4–FC_6H_4	4–ClC_6H_4	5	63	3.4
9	**5i**	4–FC_6H_4	4–$O_2NC_6H_4$	5	65	3.3
10	**5j**	4–FC_6H_4	4–MeC_6H_4	8	71	14.2
11	**5k**	4–FC_6H_4	2,4–$Cl_2C_6H_3$	4	65	1.6
12	**5l**	4–FC_6H_4	3–$O_2NC_6H_4$	6	66	6.7
13	**5m**	4–FC_6H_4	4–FC_6H_4	5	74	7.1
14	**5n**	4–FC_6H_4	C_6H_5	12	77	14.7
15	**5o**	4–ClC_6H_4	4–ClC_6H_4	6	69	6.6
Isoniazid						0.4
Rifampicin						0.1
Ciprofloxacin						4.7
Ethambutol						7.6

[a] Yield of isolated product.

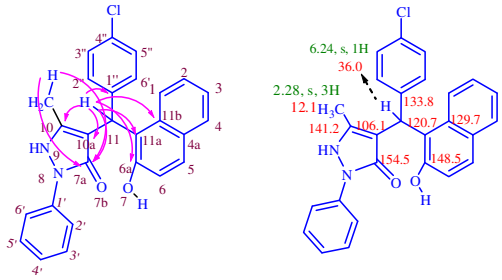


Fig. 2. HMBCs, ^1H and ^{13}C NMR chemical shifts of **5c**.

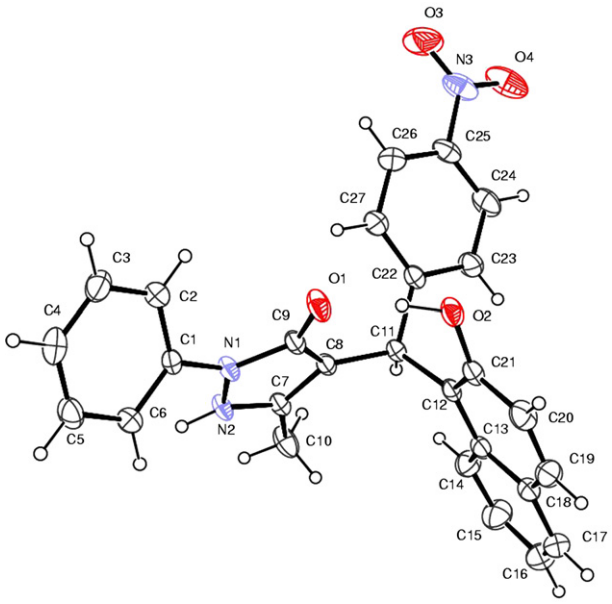
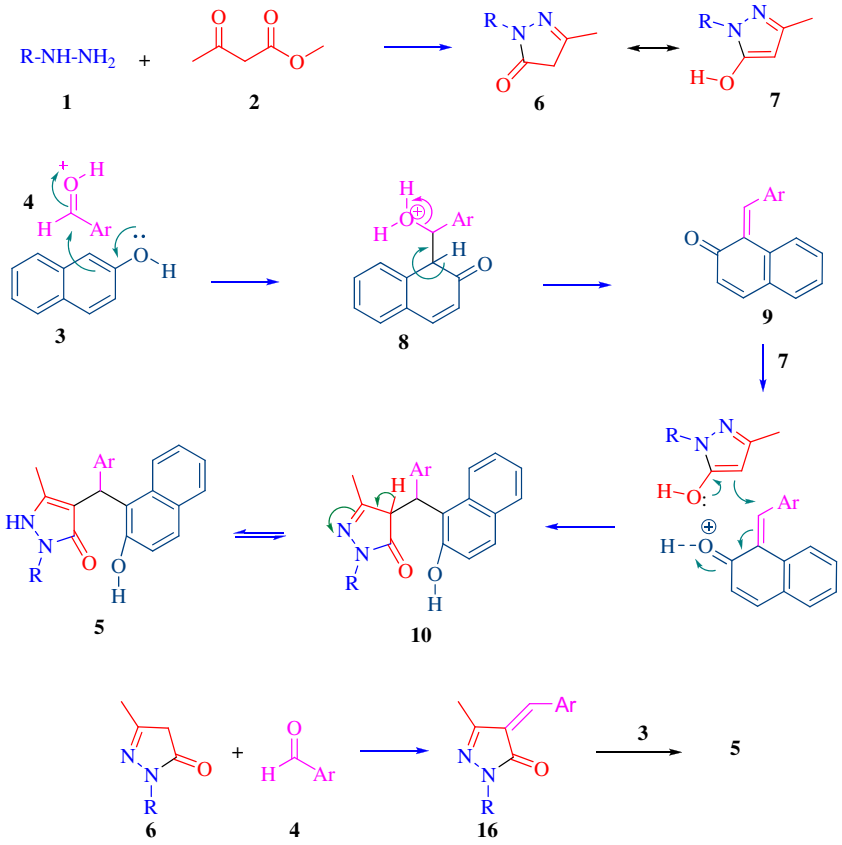


Fig. 3. ORTEP diagram of **5a**.

realised for reactions in water relative to organic solvents [32]. It is pertinent to note that multi-component domino/sequential reactions are characterized by elegance and convergence resulting in rapid building up of molecular complexity and diversity, besides affording good yields and selectivity [33]. In these reactions, the intermediates are not isolated and purified as they undergo further reactions *in situ* resulting in maximization of the yield and consequent minimization of the waste rendering the protocols eco-friendly [34].

Initially, the reaction was investigated in different solvents and catalysts (Table 1) as well as under solvent-free conditions with a view to maximizing the yield of the product. The reaction in the absence of catalyst either in water or under solvent-free condition failed to afford the product (entries 1 and 7). In presence of *p*-TSA, the reaction afforded a maximum yield of the product in water (entry 2), while no product could be obtained in chloroform (entry 5). In the presence of Lewis acid, $InCl_3$, the reaction failed to occur in water (entry 11), while under solvent-free condition a yield of 40% was obtained (entry 12) disclosing that water, being abundantly available, in the reaction mixture coordinates to the catalyst and diminishes its catalytic activity. In other solvents, in presence of $InCl_3$, the yield varied from 15 to 33% (entries 8–10). The montmorillonite K-10 catalyst failed to effect the reaction either in water or under solvent-free condition (entries 16 and 17), while the yield was maximum (48%) in acetonitrile. From the above, it is very clear that the most suitable catalyst-solvent combination, among those examined, is *p*-TSA-water for the reaction to afford a maximum yield of the product. Hence this solvent-catalyst combination was used for all subsequent experiments taking equimolar amounts of substituted hydrazine **1**, methyl acetoacetate **2**, β-naphthol **3** and aromatic aldehydes **4a–i** in water at reflux in the presence of 10 mol % *p*-TSA (Scheme 1). In a typical reaction, a mixture of substituted hydrazine **1** and methyl acetoacetate **2** was allowed to react for 50–60 min to which aromatic aldehyde and β-naphthol were added and the reaction allowed to completion (TLC). By this sequential method, the yield of the final product was found to be more with a lower impurity profile than when the reaction was performed by mixing all the reactants in one instance. Hence the optimized four-component sequential methodology was followed



Scheme 2. Mechanism for the formation 2-aryl-5-methyl-2,3-dihydro-1*H*-3-pyrazolones **5**.

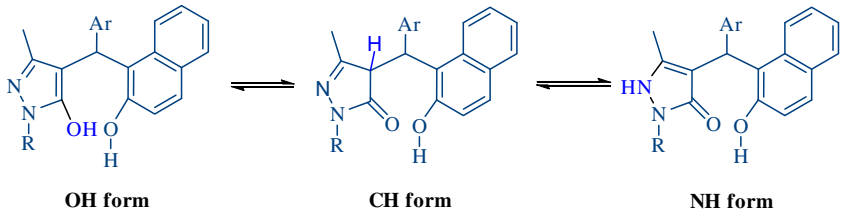


Fig. 4. Tautomeric forms of pyrazolone **5**.

throughout and the product isolated in good yields (58–77%; Table 2) from the reaction mixture via purification by column chromatography.

The structure of 2-aryl-5-methyl-2,3-dihydro-1*H*-3-pyrazolones **5** is in accord with elemental analysis and NMR spectroscopic data as illustrated for a representative example, **5c**. In the ^{1}H NMR spectrum, the H-11 gives a singlet at 6.24 ppm, which shows (i) a C,H-COSY correlation with carbon signal at 36.0 ppm, assigning it to C-11 and (ii) HMBCs (Fig. 2) with C-10a, C-11a, C-11b, C-1″, C-10, C-**6a** and C-**7a** at 106.1, 120.7, 128.7, 133.8, 141.2, 148.5 and 154.0 ppm respectively. The methyl hydrogens of the pyrazole sub-structure appear as a singlet at 2.28 ppm and its carbon signal occurs at 12.1 ppm. The methyl hydrogens show HMBCs with the signals at 106.1 and 154.0 ppm due to C-10a and C-7a respectively. The structure of **5c** determined from NMR spectroscopic studies was further confirmed by a single crystal X-ray crystallographic study [35] of **5a** (Fig. 3).

The sequential reactions presumably proceed through the mechanism depicted in Scheme 2 via the initial reaction of arylhydrazines **1** with methyl acetoacetate **2** to afford the pyrazolones **6** [36], which could be in equilibrium with their tautomers **7**. In another reaction, β-naphthol upon nucleophilic addition to aldehydes with concomitant dehydration presumably results in the formation of α,β-unsaturated ketone **9.** Subsequent Michael addition of **7** over α,β-unsaturated ketone **9** results in formation of pyrazolone **10**. An alternative reaction pathway via the formation of intermediate **16**, followed by its reaction with β-naphthol affording **5** remains a possibility. Our efforts to isolate **16** (Ar = *p*–ClC_6H_4) from (i) the two-component reaction of **6** and *p*-chlorobenzaldehyde and (ii) the three-component reaction of phenylhydrazine with methyl acetoacetate **2** and *p*-chlorobenzaldehyde in water in presence of *p*-TSA did not fructify. These reactions, instead, led to **12** (Ar = *p*–ClC_6H_4). Similarly, the reaction of equimolar amounts of β-naphthol and *p*-chlorobenzaldehyde was performed with a view to getting **9**. Interestingly, this reaction resulted in the formation of **15** (Ar = *p*–ClC_6H_4) along with 50% of unreacted *p*-chlorobenzaldehyde, wherein **9** could not be detected even in traces. These results show that both intermediates **16** and **9** in the above reactions are very reactive towards the subsequent reactions with pyrazolone and β-naphthol respectively. Hence information on the relative rates of formation as well as further reactions of **16** and **9** with β-naphthol or pyrazolone respectively could not be obtained and compared. Consequently, whether the sequential reactions occur through the intermediate **16** or **9** it could not be ascertained in the present study.

It is seen from a previous report [37] that pyrazolone could exist in three tautomeric forms, *viz.* the CH, OH and NH forms (Fig. 4). The structure of **5**, elucidated by NMR spectroscopic and X-ray crystallographic data, reveals that after the Michael addition, tautomerisation occurs to afford pyrazolones **5** in the NH form.

The intermediacy of pyrazolone **6** in this sequential transformation is evident from the fact that **6** prepared in a separate reaction of phenylhydrazine with methyl acetoacetate, when subjected to reaction with 4-chlorobenzaldehyde **4c** and β-naphthol **3** afforded **5c** in shorter time duration (by 60 min) than the overall four-component sequential reaction that affords **5c**. It is pertinent to note that the condensation products of aldehyde with 2 mol of either pyrazolone affording **12** [38] or β-naphthol **3** leading to **13** [39] or their further annulated products **14** [40] or **15** [41] are not formed (Fig. 5) in this sequential four-component reaction under the experimental conditions employed, rendering the transformation product-selective.

3. Biological results and discussion

All the newly synthesized compounds were screened for their *in-vitro* antimycobacterial activity against MTB in Middlebsook 7H11 agar medium supplemented with OADC by agar dilution method similar to that recommended by the National Committee

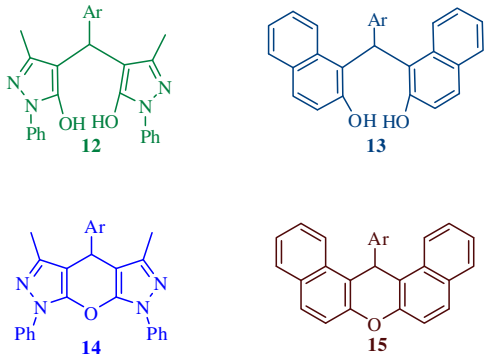


Fig. 5. Condensation products of aromatic aldehyde with pyrazolone/2-naphthol.

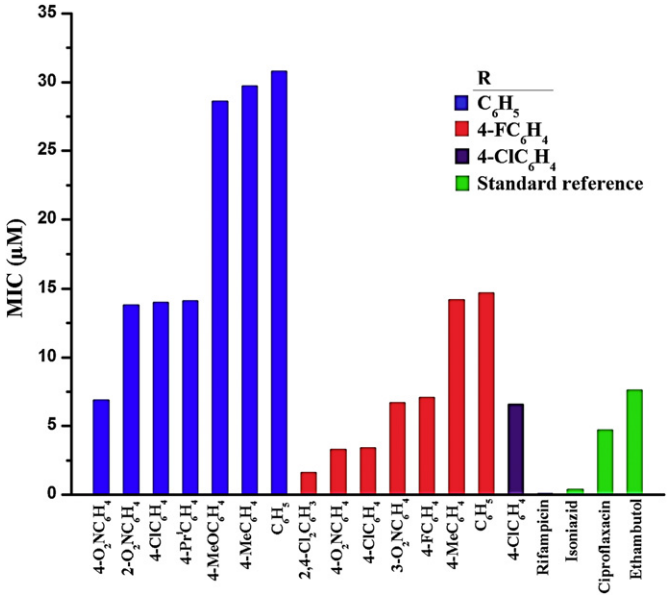


Fig. 6. Comparison of MIC (μM) values of series 5 and standard drugs.

for Clinical Laboratory Standards for the determination of MIC in duplicate [42]. The MIC is defined as the minimum concentration of compounds required to inhibit 99% of bacterial growth. The MIC of synthesized compounds determined in duplicate measured at 7.4 pH along with that of standard drugs are listed in Table 2. All the fifteen compounds showed good *in-vitro* activity with MIC ranging from 1.6 to 30.8 μM.

An examination of the MIC (μM) values of series **5** and standard drugs shown in Fig. 6 show that seven compounds, *viz.* **5a**, **5h**, **5i**, **5k**, **5l**, **5m** and **5o** were more active against MTB than the first line anti-TB drug ethambutol (MIC 7.6 μM), whilst three of them, *viz.* **5k**, **5i** and **5h** were more potent than ciprofloxacin (MIC 4.7). However, all the compounds were less potent than rifampicin and isoniazid against MTB. The compound, 4-[(2,4-dichlorophenyl)(2-hydroxy-1-naphthyl)methyl]-2-(4-fluorophenyl)-5-methyl-2,3 dihydro-1*H*-3-pyrazolone (**5k**) displayed the maximum potency with a minimum inhibitory concentration (MIC) of 1.6 μM against MTB, being 2.94 and 4.75 times more active than ciprofloxacin and ethambutol respectively.

With respect to structure-MTB activity relationship, the data in Table 2 show that the substituent on the *N*-aryl ring of 2-aryl-5-methyl-2,3-dihydro-1*H*-3-pyrazolones **5** has a profound effect on the antimycobacterial activity, activity order being: $4{-}FC_6H_4 > 4{-}ClC_6H_4 > C_6H_5$. In general, aryl ring at C-11 bearing electron-withdrawing groups such as halogens and nitro show greater activity than that with electron-releasing groups, *viz.* methoxy, methyl and isopropyl. In particular, among the pyrazolones with nitrogen bearing 4-flourophenyl ring **5h** − **5n**, the order of activity with respect to aryl ring linked to C-11 is found to be: $2,4{-}Cl_2C_6H_3 > 4{-}O_2NC_6H_4 > 4{-}ClC_6H_4 > 3{-}O_2NC_6H_4 > 4{-}FC_6H_4 > 4{-}MeC_6H_4 > C_6H_5$. Similarly, in pyrazolones **5a**–**5g,** with a phenyl ring linked to nitrogen, the influence of the aryl at C-11 lies in the order: $4{-}O_2NC_6H_4 > 2{-}O_2NC_6H_4 > 4{-}Pr^iC_6H_4 > 4{-}ClC_6H_4 > 4{-}MeOC_6H_4 > MeC_6H_4 > C_6H_5$. The compound **5k** with one fluorine and two chlorines in the aryl rings displayed the maximum potency with MIC of 1.6 μM against MTB.

4. Conclusion

In conclusion, the present work describes a one-pot, convergent, expedient sequential protocol for the synthesis of 2-aryl-5-methyl-2,3-dihydro-1*H*-3-pyrazolones from the reaction of arylhydrazine, methyl acetoacetate, aromatic aldehydes and β-naphthol in the presence of *p*-TSA in water under mild reaction conditions in good yields. These compounds displayed significant *in-vitro* anti-mycobacterial activity against MTB.

5. Experimental

The melting points were measured in open capillary tubes and are uncorrected. The ^1H, ^{13}C and the 2D NMR spectra were recorded on a Bruker (Avance) 300 MHz NMR instrument using TMS as internal standard and $CDCl_3$ as solvent. Standard Bruker software was used throughout. Chemical shifts are given in parts per million (δ-scale) and the coupling constants are given in Hertz. Silica gel-G plates (Merck) were used for TLC analysis with a mixture of petroleum ether (60–80 °C) and ethyl acetate as eluent. Elemental analyses were performed on a Perkin Elmer 2400 Series II Elemental CHNS analyzer.

5.1. General procedure for the synthesis of 2-aryl-5-methyl-2,3-dihydro-1H-3-pyrazolones (*5*)

To a mixture of phenylhydrazine (1 mmol) and methyl acetoacetate (1 mmol) in water (4 ml) stirred at room temperature for 50–60 min, aromatic aldehyde (1 mmol), β-naphthol (1 mmol) and *p*-TSA (0.1 mmol) were added and heated to reflux for the time given in Table 2. After completion of the reaction (TLC), the reaction mixture was extracted with ethyl acetate (2 × 40 ml). After removal of the solvent, the residue was chromatographed over silica gel (230–400 mesh) using petroleum ether-ethyl acetate mixture (4:1 v/v), which afforded the pure product **5**.

5.1.1. 4-(2-Hydroxy-1-naphthyl)[4-(nitromethyl)phenyl]methyl-5-methyl-2-phenyl-2,3-dihydro-1H-3-pyrazolone (*5a*)

(Table 2, entry, 1): Yellow solid; yield: 75%, m.p 207 °C; ^1H NMR (300 MHz, DMSO-d_6) δ_H: 2.22 (s, 3H, CH_3), 6.28 (s, 1H, CH), 7.10–7.14 (m, 1H, Ar–H), 7.20–7.27 (m, 1H, Ar–H), 7.29–7.34 (m, 3H, Ar–H), 7.41–7.48 (m, 3H, Ar–H), 7.68–7.72 (m, 2H, Ar–H), 7.76–7.79 (m, 1H, Ar–H), 7.81–7.85 (m, 1H, Ar–H), 8.10–8.13 (m, 2H, Ar–H), 8.20–8.22 (m, 1H, Ar–H), 10.82 (bs, 1H, OH); ^{13}C NMR (75 MHz DMSO-d_6) δ_C: 12.0, 36.8, 105.3, 119.9, 120.3, 121.0, 123.0, 123.3, 123.4, 125.7, 126.9, 129.0, 129.1, 129.4, 129.5, 133.7, 137.0, 146.0, 148.5, 151.2, 153.9. Anal. Calcd for $C_{27}H_{21}N_3O_4$: C, 71.83; H, 4.69; N, 9.31; Found: C, 71.73; H, 4.62; N, 9.23%.

5.1.2. 4-[(2-Hydroxy-1-naphthyl)(2-nitrophenyl)methyl]-5-methyl-2-phenyl-2,3-dihydro-1H-3-pyrazolone (*5b*)

(Table 2, entry, 2): Yellow solid; yield: 72%, m.p 157 °C; ^1H NMR (300 MHz, DMSO-d_6) δ_H: 1.94 (s, 3H, CH_3), 6.69 (s, 1H, CH), 7.03 (d, 1H, J = 8.7 Hz, Ar–H), 7.19–7.29 (m, 3H, Ar–H), 7.39–7.44 (m, 4H, Ar–H & NH), 7.54 (t, 1H J = 7.8 Hz, Ar–H), 7.67–7.79 (m, 6H, Ar–H), 8.02 (d, 1H, J = 8.7 Hz Ar–H), 10.88 (bs, 1H, OH); ^{13}C NMR (75 MHz DMSO-d_6) δ_C: 11.8, 33.6, 105.1, 118.1, 119.5, 120.0, 122.9, 123.2, 124.5, 125.4, 127.0, 127.5, 128.9, 129.0, 129.4, 130.5, 132.5, 134.0, 136.6, 137.4, 148.7, 149.9, 153.6. Anal. Calcd for $C_{27}H_{21}N_3O_4$: C, 71.83; H, 4.69; N, 9.31; Found: C, 71.91; H, 4.76; N, 9.41%.

5.1.3. 4-[(4-Chlorophenyl)(2-hydroxy-1-naphthyl)methyl]-5-methyl-2-phenyl-2,3-dihydro-1H-3-pyrazolone (*5c*)

(Table 2, entry, 3): Yellow solid; yield: 74%, m.p 176 °C; ^1H NMR (300 MHz, DMSO-d_6) δ_H: 2.28 (s, 3H, CH_3), 6.24 (s, 1H, CH), 7.12–7.18 (m, 3H, Ar–H), 7.27–7.34 (m, 4H, Ar–H), 7.48–7.54 (m, 3H, Ar–H), 7.75–7.83 (m, 3H, Ar–H), 7.89 (d, 1H, J = 8.4 Hz, Ar–H), 8.28 (d, 1H, J = 8.4 Hz, Ar–H), 10.87 (bs, 1H, OH); ^{13}C NMR (75 MHz DMSO-d_6) δ_C: 12.1, 36.0, 106.1, 119.9, 120.7, 121.2, 122.9, 123.3, 125.7, 126.8, 128.1, 129.0, 129.1, 129.2, 129.4, 129.7, 130.4, 133.8, 137.0, 141.2, 148.5, 154.0. Anal. Calcd for $C_{27}H_{21}ClN_2O_2$: C, 73.55; H, 4.80; N, 6.35; Found: C, 73.63; H, 4.89; N, 6.28%.

5.1.4. 4-[(2-Hydroxy-1-naphthyl)(phenyl)methyl]-5-methyl-2-phenyl-2,3-dihydro-1H-3-pyrazolone (*5d*)

(Table 2, entry, 4): White solid; yield: 62%, m.p 205 °C; ^1H NMR (300 MHz, DMSO-d_6) δ_H: 2.19 (s, 3H, CH_3), 6.18 (s, 1H, CH), 7.07–7.10 (m, 4H, Ar–H), 7.10–7.19 (m, 5H, Ar–H) 7.25–7.28 (m, 3H, Ar–H), 7.68–7.80 (m, 4H, Ar–H & NH), 8.21 (s, 1H, Ar–H), 10.77 (bs, 1H, OH); ^{13}C NMR (75 MHz DMSO-d_6) δ_C 16.8, 41.1, 124.5, 125.7, 125.9, 127.5, 128.0, 130.3, 130.6, 131.4, 132.5, 132.9, 133.7, 133.8, 134.1, 138.7, 141.7, 146.6, 153.2, 158.8. Anal. Calcd for $C_{27}H_{22}N_2O_2$ C, 79.78; H, 5.46; N, 6.89; Found: C, 79.70; H, 5.53; N, 6.79%.

5.1.5. 4-[(2-Hydroxy-1-naphthyl)(4-isopropylphenyl)methyl]-5-methyl-2-phenyl-2,3-dihydro-1H-3-pyrazolone (*5e*)

(Table 2, entry, 5): Viscous liquid; yield: 59%. ^1H NMR (300 MHz, $CDCl_3$) δ_H: 1.08 (d, 6H, J = 6.9 Hz, $2CH_3$), 2.09 (s, 3H, CH_3), 2.69–2.73 (m, 1H, CH), 5.97 (s, 1H, CH), 6.79–6.90 (m, 3H, Ar–H), 6.97–7.14 (m, 7H, Ar–H & NH), 7.25–7.35 (m, 2H, Ar–H), 7.46 (t, 1H, J = 8.4 Hz, Ar–H), 7.64 (d, 1H, J = 8.9 Hz, Ar–H), 7.80 (d, 1H, J = 8.4 Hz, Ar–H), 8.02 (d, 1H J = 8.9 Hz, Ar–H), 10.67 (bs, 1H, OH); ^{13}C NMR (75 MHz $CDCl_3$) δ_C: 11.2, 23.8, 33.4, 35.7, 106.3, 120.3, 121.5, 121.7, 122.4, 126.1,

126.4, 126.9, 128.7, 129.0, 129.1, 129.5, 133.7, 134.9, 137.7, 146.3, 146.5, 153.7, 162.1. Anal. Calcd for $C_{30}H_{28}N_2O_2$: C, 80.33; H, 6.29; N, 6.25. Found: C, 80.43; H, 6.22; N, 6.16%.

*5.1.6. 4-[(2-Hydroxy-1-naphthyl)(4-methoxyphenyl)methyl]-5-methyl-2-phenyl-2,3-dihydro-1H-3-pyrazolone (**5f**)*

(Table 2, entry, 6): White solid; yield: 63%, m.p 184 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ_H: 2.16 (s, 3H, CH_3), 3.67 (s, 3H, OCH_3), 6.09 (s, 1H, CH), 6.74–6.80 (m, 2H, Ar–H), 6.92–6.95 (m, 2H, Ar–H), 7.04–7.07 (m, 1H, Ar–H), 7.22–7.27 (m, 2H, Ar–H), 7.41–7.44 (m, 3H, Ar–H), 7.64–7.71 (m, 3H, Ar–H), 7.77–7.80 (m, 1H, Ar–H), 8.18 (s, 1H, Ar–H), 10.89 (bs, 1H, OH); ^{13}C NMR (75 MHz DMSO-d_6) δ_C: 11.4, 34.9, 54.6, 106.4, 112.9, 119.0, 120.3, 122.0, 122.5, 124.8, 125.9, 128.1, 128.2, 128.3, 128.6, 132.8, 133.2, 136.3, 147.8, 148.7, 153.3, 156.8. Anal. Calcd for $C_{28}H_{24}N_2O_3$: C, 77.04; H, 5.54; N, 6.42; Found: C, 77.13; H, 5.62; N, 6.35%.

*5.1.7. 4-[(2-Hydroxy-1-naphthyl)(4-methylphenyl)methyl]-5-methyl-2-phenyl-2,3-dihydro-1H-3-pyrazolone (**5g**)*

(Table 2, entry 7): White solid; yield: 58%, m.p. 179 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ_H : 2.27 (s, 3H, CH_3), 2.46 (s, 3H, CH_3), 6.09 (s, 1H, CH), 7.01–7.08 (m, 4H, Ar–H), 7.15–7.21 (m, 2H, Ar–H), 7.30–7.41 (m, 4H, Ar–H & NH), 7.50 (t, 1H, J = 7.5 Hz, Ar–H), 7.69–7.71 (m, 3H, Ar–H), 7.81 (d, 1H, J = 7.5 Hz, Ar–H), 8.15 (d, 1H, J = 9.0 Hz, Ar–H), 10.81 (bs, 1H, OH); ^{13}C NMR (75 MHz DMSO-d_6) δ_C 11.9, 21.0, 35.9, 106.5, 120.1, 121.2, 121.6, 122.5, 125.6, 126.5, 127.4, 128.7, 128.8, 128.9, 129.0, 129.1, 129.8, 133.8, 134.7, 136.6, 138.3, 147.7, 154.0, 162.4. Anal. Calcd for $C_{28}H_{24}N_2O_2$: C, 79.98; H, 5.75; N, 6.66; Found: C, 79.88; H, 5.83; N, 6.73%.

*5.1.8. 4-[(4-Chlorophenyl)(2-hydroxy-1-naphthyl)methyl]-2-(4-fluorophenyl)-5-methyl-2,3-dihydro-1H-3-pyrazolone (**5h**)*

(Table 2, entry 8): White solid; yield: 63%, m.p. 159 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ_H: 2.31 (s, 3H, CH_3), 6.02 (s, 1H, CH), 6.80–6.86 (m, 2H, Ar–H), 7.02–7.07 (m, 3H, Ar–H), 7.10–7.12 (m, 3H, Ar–H), 7.26–7.30 (m, 2H, Ar–H & NH), 7.37 (t, 1H, J = 7.5 Hz, Ar–H), 7.53 (t, 1H, J = 7.5 Hz, Ar–H), 7.69 (d, 1H, J = 8.7 Hz, Ar–H), 7.83 (d, 1H, J = 8.7 Hz, Ar–H), 8.05 (d, 1H, J = 8.7 Hz, Ar–H), 10.90 (bs, 1H, OH); ^{13}C NMR (75 MHz $CDCl_3$) δ_C: 11.8, 35.6, 106.3, 114.4, 114.7, 115.2, 115.7, 121.4, 121.8, 122.2, 122.4, 122.5, 122.8, 126.5, 128.5, 128.8, 129.2, 132.6, 133.8, 136.5, 146.9, 153.6, 161.9. Anal. Calcd for $C_{27}H_{20}ClFN_2O_2$: C, 70.66; H, 4.39; N, 6.10; Found: C, 70.59; H, 4.49; N, 6.18%.

*5.1.9. 2-(4-Fluorophenyl)-4-(2-hydroxy-1-naphthyl)[4-(nitromethyl) phenyl]methyl-5-methyl-2,3-dihydro-1H-3-pyrazolone (**5i**)*

(Table 2, entry 9): White solid; yield: 65%, m.p. 172 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ_H: 2.13 (s, 3H, CH_3), 6.25 (s, 1H, CH), 7.09 (d, 1H, J = 9.0 Hz, Ar–H), 7.25–7.30 (m, 5H, Ar–H), 7.41 (t, 1H, J = 7.2 Hz, Ar–H), 7.66–7.70 (m, 2H, Ar–H), 7.73 (d, 1H, J = 8.7 Hz, Ar–H), 7.81 (d, 1H, J = 8.4 Hz, Ar–H,), 8.07–8.16 (m, 2H, Ar–H), 8.26 (s, 1H, Ar–H), 10.93 (bs, 1H, OH); ^{13}C NMR (75 MHz DMSO-d_6) δ_C: 16.7, 41.5, 109.8, 120.7, 121.0, 124.9, 125.5, 126.9, 127.0, 127.7, 128.1, 131.6, 133.8, 134.2, 138.3, 150.6, 153.3, 155.9, 158.5, 162.9, 166.1. Anal. Calcd for $C_{27}H_{20}FN_3O_4$: C, 69.08; H, 4.29; N, 8.95; Found: C, 69.15; H, 4.39; N, 8.89%.

*5.1.10. 2-(4-Fluorophenyl)-4-[(2-hydroxy-1-naphthyl)(4-methylphenyl)methyl]-5-methyl-2,3-dihydro-1H-3-pyrazolone (**5j**)*

(Table 2, entry 10): Yellow solid; yield: 71%, m.p. 183 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ_H: 2.26 (s, 3H, CH_3), 2.42 (s, 3H, CH_3), 6.09 (s, 1H, CH), 7.03–7.16 (m, 6H, Ar–H & NH), 7.15 (d, 1H, J = 8.7 Hz, Ar–H), 7.32–7.35 (m, 1H, Ar–H), 7.44–7.52 (m, 2H, Ar–H), 7.67–7.70 (m, 3H, Ar–H), 7.79 (d, 1H, J = 5.4 Hz, Ar–H), 8.15 (d, 1H, J = 5.4 Hz, Ar–H), 10.81 (bs, 1H, OH); ^{13}C NMR (75 MHz $CDCl_3$) δ_C: 11.0, 20.0, 35.0, 106.5, 114.6, 114.9, 120.7, 120.9, 121.6, 125.5, 126.1, 127.8, 127.9, 128.1, 128.4, 132.1, 132.8, 134.2, 137.2, 146.2, 157.7, 160.9. Anal. Calcd for $C_{28}H_{23}FN_2O_2$: C, 76.69; H, 5.29; N, 6.39; Found: C, 76.80; H, 5.20; N, 6.45%.

*5.1.11. 4-[(2,4-Dichlorophenyl)(2-hydroxy-1-naphthyl)methyl]-2-(4-fluorophenyl)-5-methyl-2,3-dihydro-1H-3-pyrazolone (**5k**)*

(Table 2, entry 11): White solid; yield: 65%, m.p. 198 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ_H : 2.30 (s, 3H, CH_3), 6.12 (s, 1H, CH), 7.07–7.17 (m, 2H, Ar–H), 7.26–7.33 (m, 2H, Ar–H), 7.48–7.50 (m, 2H, Ar–H & NH), 7.57–7.59 (m, 2H, Ar–H), 7.64–7.72 (m, 4H, Ar–H), 7.78 (d, 1H, J = 8.1 Hz, Ar–H), 8.06 (d, 1H, J = 8.1 Hz, Ar–H), 10.78 (bs, 1H, OH); ^{13}C NMR (75 MHz $CDCl_3$) δ_C: 12.0, 36.4, 106.2, 116.0, 116.4, 120.0, 121.0, 121.1, 122.1, 122.4, 123.0, 123.4, 127.0, 129.0, 129.1, 129.5, 129.7, 133.7, 135.0, 144.9, 148.0, 149.0, 153.9, 161.4. Anal. Calcd for $C_{27}H_{19}Cl_2FN_2O_2$: C, 65.73; H, 3.88; N, 5.68; Found: C, 65.65; H, 3.80; N, 5.78%.

*5.1.12. 2-(4-Fluorophenyl)-4-[(2-hydroxy-1-naphthyl)(3-nitrophenyl)methyl]-5-methyl-2,3-dihydro-1H-3-pyrazolone (**5l**)*

(Table 2, entry 12): White solid; yield: 66%, m.p. 148 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ_H: 2.21 (s, 3H, CH_3), 6.31 (s, 1H, CH), 7.11–7.20 (m, 1H, Ar–H), 7.30–7.34 (m, 3H, Ar–H), 7.42–7.47 (m, 1H, Ar–H), 7.53–7.55 (m, 2H, Ar–H), 7.70–7.91 (m, 5H, Ar–H), 8.04–8.10 (m, 1H, Ar–H), 8.22–8.31 (m, 1H, Ar–H), 10.71 (bs, 1H, OH); ^{13}C NMR (75 MHz DMSO-d_6) δ_C: 16.8, 41.1, 120.8, 121.1, 124.8, 125.8, 126.9, 127.1, 127.8, 128.1, 131.7, 133.8, 133.9, 134.3, 134.7, 138.4, 139.7, 149.7, 152.8, 153.4, 158.6, 162.9, 166.1. Anal. Calcd for $C_{27}H_{20}FN_3O_4$: C, 69.08; H, 4.29; N, 8.95; Found: C, 69.02; H, 4.20; N, 8.85%.

*5.1.13. 2-(4-Fluorophenyl)-4-[(4-fluorophenyl)(2-hydroxy-1-naphthyl)methyl]-5-methyl-2,3-dihydro-1H-3-pyrazolone (**5m**)*

(Table 2, entry 13): White solid; yield: 74%, m.p. 183 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ_H: 2.26 (s, 3H, CH_3), 6.01 (s, 1H, CH), 6.72–6.80 (m, 2H, Ar–H), 6.81–6.87 (m, 2H, Ar–H), 7.01–7.07 (m, 3H, Ar–H), 7.15–7.20 (m, 2H, Ar–H),), 7.36 (t, 1H, J = 10.2 Hz, Ar–H), 7.51 (t, 1H, J = 7.2 Hz, Ar–H)), 7.68 (d, 1H, J = 9.0 Hz, Ar–H)), 7.82 (d, 1H, J = 7.2 Hz, Ar–H), 8.04 (d, 1H, J = 9.0 Hz, Ar–H), 10.91 (bs, 1H, OH); ^{13}C NMR (75 MHz $CDCl_3$) δ_C: 11.8, 35.6, 105.9, 114.4, 114.8, 115.5, 115.7, 121.4, 121.5, 122.4, 122.5, 122.6, 126.5, 128.5, 128.6, 129.0, 129.2, 133.5, 136.6, 147.9, 162.3. Anal. Calcd for $C_{27}H_{20}F_2N_2O_2$: C, 73.29; H, 4.56; N, 6.33; Found: C, 73.39; H, 4.62; N, 6.22%.

*5.1.14. 2-(4-Fluorophenyl)-4-[(2-hydroxy-1-naphthyl)(phenyl) methyl]-5-methyl-2,3-dihydro-1H-3-pyrazolone (**5n**)*

(Table 2, entry 14): White solid; yield: 77%, m.p. 192 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ_H: 2.31 (s, 3H, CH_3), 6.10 (s, 1H, CH), 6.84–6.91 (m, 2H, Ar–H), 7.08–7.13 (m, 6H, Ar–H), 7.31–7.38 (m, 3H, Ar–H), 7.50 (t, 1H, J = 7.5 Hz, Ar–H), 7.75 (d, 1H, J = 8.7 Hz, Ar–H), 7.83 (d, 1H, J = 7.5 Hz, Ar–H), 8.06 (d, 1H, J = 8.7 Hz, Ar–H), 10.78 (bs, 1H, OH); ^{13}C NMR (75 MHz $CDCl_3$) δ_C: 12.1, 36.4, 105.8, 115.9, 116.2, 121.0, 121.2, 122.0, 122.1, 122.7, 123.2, 125.8, 126.6, 127.8, 128.2, 129.0, 133.5, 134.0, 142.1, 148.5, 154.1, 158.2, 161.4. Anal. Calcd for $C_{27}H_{21}FN_2O_2$: C, 76.40; H, 4.99; N, 6.60; Found: C, 76.33; H, 4.91; N, 6.70%.

*5.1.15. 2-(4-Chlorophenyl)-4-[(4-chlorophenyl)(2-hydroxy-1-naphthyl)methyl]-5-methyl-2,3dihydro-1H-3-pyrazolone (**5o**)*

(Table 2, entry, 15): Yellow solid; yield: 69%, m.p. 153 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ_H: 2.26 (s, 3H, CH_3), 6.09 (s, 1H, CH), 7.01–7.10 (m, 6H, Ar–H & NH), 7.19–7.22 (m, 2H, Ar–H), 7.26–7.30 (m, 2H, Ar–H), 7.36 (t, 1H, J = 7.2 Hz, Ar–H), 7.55 (t, 1H, J = 7.2 Hz, Ar–H), 7.68 (d, 1H, J = 8.7 Hz, Ar–H), 7.82 (d, 1H, J = 8.7 Hz, Ar–H), 8.06 (d, 1H, J = 8.7 Hz, Ar–H), 10.73 (bs, 1H, OH); ^{13}C NMR (75 MHz DMSO-d_6) δ_C: 13.2, 35.7, 106.1, 120.0, 121.3, 122.3, 123.1, 126.8, 127.0, 127.7, 128.3, 128.8, 128.9, 129.0, 129.2, 129.5, 131.1, 131.8, 133.4, 134.8, 139.0, 145.6, 153.4. Anal. Calcd for $C_{27}H_{20}Cl_2N_2O_2$: C, 68.22; H, 4.24; N, 5.89; Found: C, 68.29; H, 4.34; N, 5.80%.

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Appendix. Supplementary material

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.ejmech.2011.07.029.

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