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SYNTHESIS AND EVALUATION OF NOVEL HETEROCYCLIC COMPOUND FOR ANTITUBERCULER ACTIVITY

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ABSTRACT

In last few decades, though significant progress has been made in the treatment and control strategies of tubercular infections by introducing new diagnostic and monitoring tools and combination therapy, it still continues to be severe problem. Thus with the aim of developing novel molecule with improved potency for treating *Mycobacterium tuberculosis* H37Rv strain infections and with decreased probability of developing drug resistance, herein we report the synthesis of coumarin derivatives, starting from salicyaldehyde and ethyl acetoacetate , by convential organic reaction and results of investigations of their antimycobacterial activity. Many compounds have shown promising activity while others were inactive.

KEYWORDS: Coumarin derivative, well diffusion method, elemental analysis.

INTRODUCTION

Microbial infections remain the major cause of death over the world. Emergence of multi-drug resistant to different infectious organisms like *M. tuberculosis* made the condition most alarming.[1-2] Therefore, there is an urgent demand for a new class of antimicrobial agent with a different mode of action and it led medicinal chemists to explore a wide variety of chemical structures. Coumarin based natural products comprise a large class of substance found in variety of sources, especially in green plants. Natural and synthetic coumarin derivatives have been shown to possess a diverse array of pharmacological and biochemical properties like anti-inflammatory,[3-5] antioxidant,[6-9] antitumor,[10-14] analgesic,[15] anti-coagulant,[16-19] activity. Coumarin has been recommended for treatment of a number of clinical conditions, including high protein oedema and brucellosis. It is currently undergoing clinical trials for treatment of lymphoedema following breast cancer treatment and in treatment of lung and kidney cancer and of melanoma alone or in combination with cimetidine. It has also been used for prevention of dental caries. Coumarin and some of its derivatives have been tested for treatment of schizophrenia, microcirculation disorders and angiopathic ulcers, and also for treatment of high protein oedemas in animals. Coumarin has also found use in toothpastes, antiperspirant deodorants, bath products, body lotions, face creams, fragrance creams, hair sprays, shampoos, shower gels and toilet soaps. It has been used in detergents as a brightener or bleaching agent. Other synthetic coumarin based anticancer compounds include 7-hydroxycoumarin, 6-nitro-7-hydroxycoumarin, Coumarin 3-(N aryl) sulphonamides, and 3-bromophenyl 6-acetoxymethyl-2-oxo-2*H*-benzopyran-3-carboxylate. Coumarins scavenge reactive oxygen species and suppress inflammation, edema and pain.[4]

EXPERIMENTAL

General

The nucleus and its derivatives were analyzed by different ways. The melting points were recorded on electrothermal apparatus and are uncorrected. (IR) spectra were determined on Bruker IFS-66 FTIR (Bruker Bioscience, USA) using KBr pallets and wave number (í) was reported in cm-1. ^{1}H NMR spectra on a Bruker Avance 300 MHz instrument using DMSO as solvent using TMS as internal standard; the chemical shifts (δ) were reported in ppm with coupling constants (*J*) are given in Hz. Signal multiplicities were represented by s (singlet), d (doublet), t (triplet), ds (double singlet), dd (double doublet), m (multiplet) and bs (broad singlet. Elemental analysis was performed on a Hera- cus CHN-Rapid Analyser. Analysis indicated by the symbols of the elements of functions was within ±0.4% of the theoretical values. The purity of the compounds was checked on silica gel coated Al plates (Merck).

1. Synthesis of 3-acetyl coumarin

To a cold mixture of Salicylaldehydehyde (0.2M) and ethyl acetoacetate (0.2M), 2ml of piperidine was added by rapid stirring. After 20 min thee yellowish solid separated was filtered off subsequently washed with

ethanol and was recrystallised from water: ethanol (3:7), M.P 120^0 C and yield was 83.6%.

2. Preparation of 3-aryl-1-(3-coumarinyl) propan-1-ones

A mixture of 3-acetyl coumarin and various substituted aldehydes (0.012 M) were dissolved in 10ml of n-butanol under heating; then 0.3ml glacial acetic acid and the same quantity of piperidine were added. The reaction mixture was refluxed for 4 hours and then solvent was removed in vacuum. The residue was triturated with 10ml ethanol until a precipitate formed. The precipitate was filtered off and recrystallized from appropriate solvent.

3. Synthesis of 5-(substituted) aryl-3-(3-coumarinyl)-1-phenyl-2- pyrazoline

3-aryl-1-(3-coumarinyl) -1-propan-1-ones, 0.05M and phenyl hydrazine (0.2M) were dissolved in pyridine (30ml) and refluxed for 6hrs. Reaction mixture was poured on to the crushed ice and neutralized with 2N hydrochloric acid. The precipitated solid was filtered, dried and recrystallised from appropriate solvent to afford the title compound.

Spectral Data

A_1- IR (KBr): 3650(Secondary amine), 3150 (C=C str), 3016 (Aromatic CH), 1950-1450 (Double bonded functional group), 1706 (CO str), 1639 (CN str), 1410 (Co str), 3000 (NH bending), 1250 (NH bending),
C- 70.58, H- 4.5, N-9.88; m.p 201^{o}C, % yield- 69.72, Rf-0.57

NMR: δ 10.0-10.1 1H, (NH, Pri. amine), 8.8-8.9 4H, (CH, Pyridine), 7.8-7.9 5H, (CH, Benzene), 4.6-4.8 1H, (NH, Sec. amine)

A_2- IR (KBr): 3645(Secondary amine), 3150 (C=C str), 3016 (Aromatic CH), 1950-1450 (Double bonded functional group), 1700 (CO str), 1620 (CN str), 1410 (Co str), 1400 (SO_2 bending), 3000 (NH bending), 1250 (NH bending)
C- 68.56, H- 4.65, N-9.23; m.p 151^{o}C, % yield- 80%, Rf-0.61

A_3- IR (KBr): 3650(Secondary amine), 3150 (C=C str), 3010 (Aromatic CH), 1950-1450 (Double bonded functional group), 1706 (CO str), 1639 (CN str), 1410 (Co str), 3000 (NH bending), 1250 (NH bending)
C-66.50, H- 4.12, N-10.12; m.p 151^{o}C, % yield- 84%, R_f- 0.56

A_4- IR (KBr): 3650(Secondary amine), 3150 (C=C str), 3016 (Aromatic CH), 1950-1450 (Double bonded functional group), 1706 (CO str), 1639 (CN str), 1410 (Co str), 3000 (NH bending), 1250 (NH bending)
C- 70.2, H- 4.2, N-10.18; m.p 271^{o}C, % yield- 70.82, R_f-0.52.

A_5- IR (KBr): 3650(Secondary amine), 3150 (C=C str), 3016 (Aromatic CH), 1950-1450 (Double bonded functional group), 1706 (CO str), 1639 (CN str), 1410 (Co str), 1400 (SO_2 bending), 3000 (NH bending), 1250 (NH bending)
C- 68.02, H- 4.31, N- 9.52; m.p 141^{o}C, % yield- 76, R_f-0.68.

A_6- IR (KBr): 3650(Secondary amine), 3150 (C=C str), 3016 (Aromatic CH), 1950-1450 (Double bonded functional group), 1706 (CO str), 1639 (CN str), 1410 (Co str), 3000 (NH bending), 1250 (NH bending).
C- 65.83, H- 3.77, N- 10.47; m.p 279^{o}C, % yield- 70, R_f-0.59.

Antituberculer activity

The compounds were tested in-vitro for their antituberculer activity against H_{37}Rv Strain.

METHOD

Alamar Blue Dye

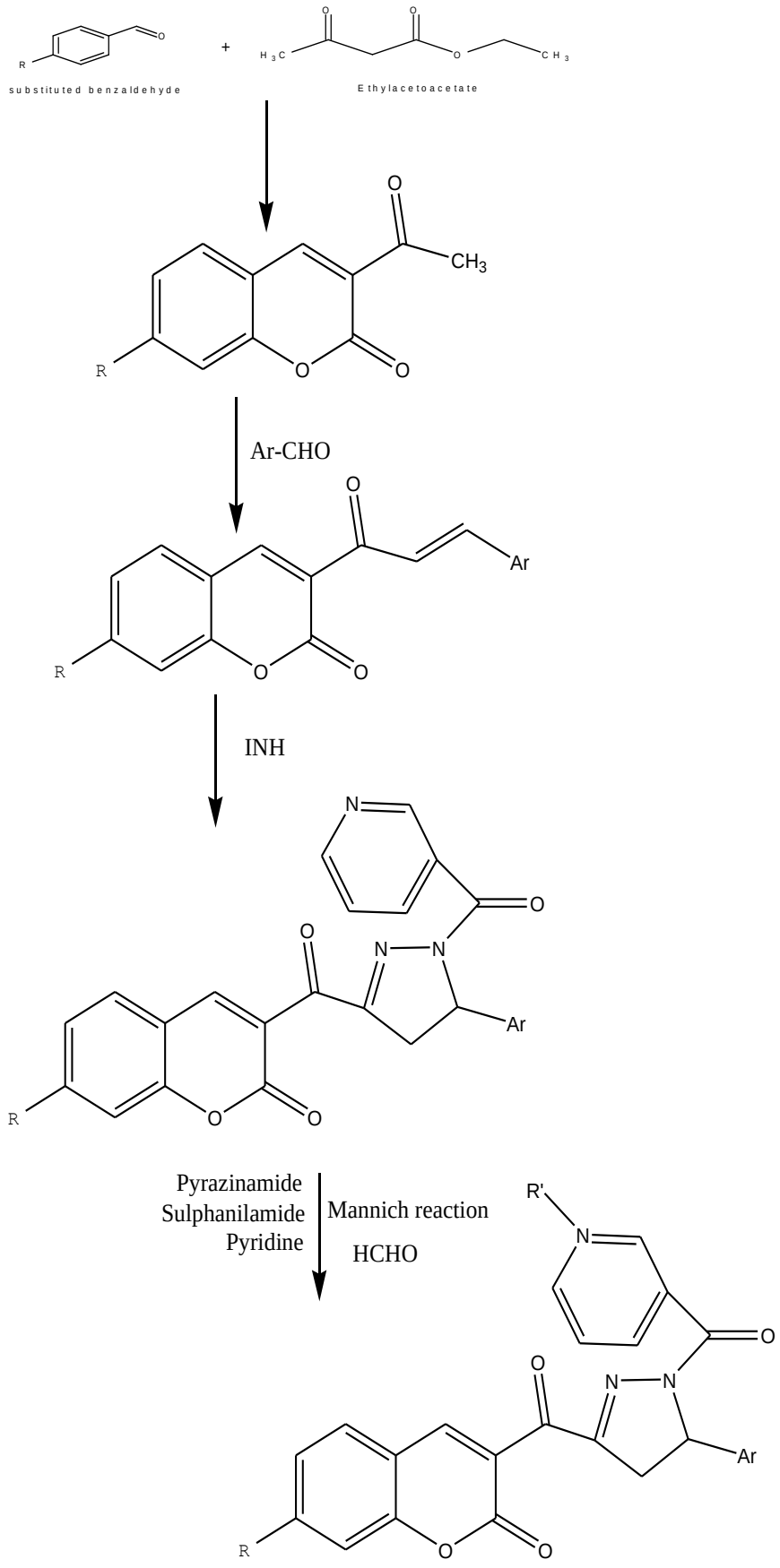
The antitubercular screening was carried out by Middle brook 7H9 agar medium against H_{37}Rv Strain. Middle brook 7H9 agar medium was inoculated with *Mycobacterium tuberculosis* of H_{37}Rv Strain. The inoculated bottles were incubated for 37°C for 4 weeks. At the end of 4 weeks they were checked for growth.

RESULT AND DISCUSSION

In the present research work, we have synthesized 6 new 5- substituted 3-aryl coumarin derivatives as explained in the scheme. The purity of the compounds was checked by TLC and melting point. Structures of these compounds were confirmed by IR, 1HNMR and elemental analysis. The synthesized compounds were subjected to anti tubercular activity by Alamar Blue Dye method against the standard streptomycin.

Compound A_1, A_3, A_6 have shown promising antituberculer activity whereas A_2, A_4, A_5 have shown moderate antituberculer activity against streptomycin at concentration of 1.6 mcg/ml by interpreting data of MIC. With the suitable molecular modification and manipulation with possible SAR studies of these compounds, promising anti microbial agents can be obtained.

Scheme: (A_1-A_6)


substituted benzaldehyde
Ethylacetoacetate
Ar-CHO
INH
Pyrazinamide
Sulphanilamide
Pyridine
Mannich reaction
HCHO

List of synthesized compounds & their IUPAC names (A_1-A_6)

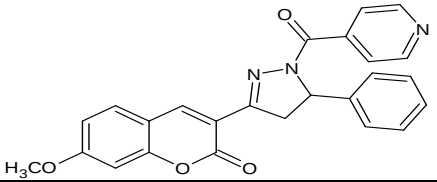
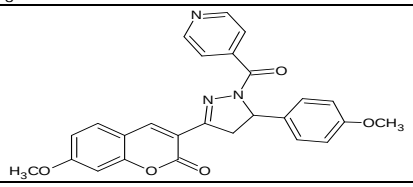
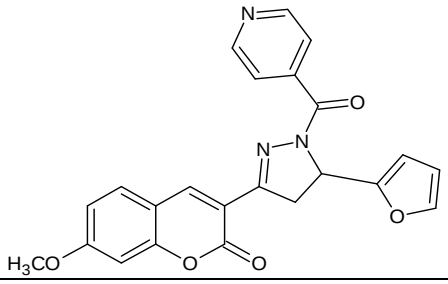
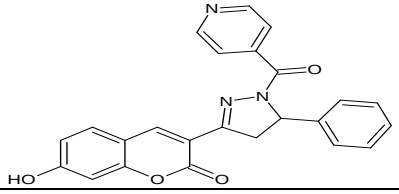
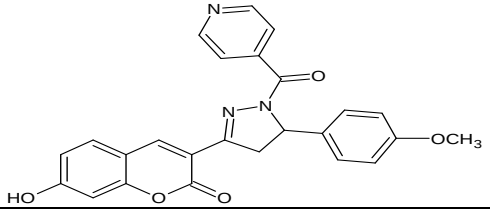
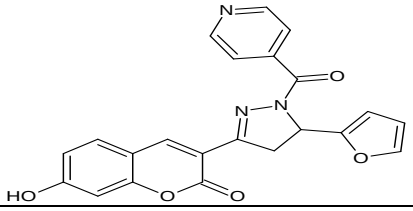
Compound	Structure	IUPAC name
A_1		3-(1-isonicotinoyl-5-phenyl-4,5-dihydro-1*H*-pyrazol-3-yl)-7methoxy-2*H*-chromen-2-one
A_2		3-[1-isonicotinoyl-5-(4methoxy phenyl)-4,5-dihydro-1*H*-pyrazol-3-yl)-7-methoxy-2*H*-chromen-2-one
A_3		3-[5-(2-furyl)-1-isonicotinoyl-4,5-dihydro-1*H*-pyrazol-3-yl]-7-methoxy-2*H*-chromen-2-one
A_4		7-hydroxy-3-(1-isonicotinoyl-5-phenyl-4,5-dihydro-1*H*-pyrazol-3-yl)-2*H*-chromen-2-one
A_5		7-hydroxy-3-[1-isonicotinoyl-5-(4methoxy phenyl)-4,5-dihydro-1*H*-pyrazol-3-yl)-2*H*-chromen-2-one
A_6		3-[5-(2-furyl)-1-isonicotinoyl-4,5-dihydro-1*H*-pyrazol-3-yl]-7-hydroxy-2*H*-chromen-2-one

Table No. 3. Anti-tuberculer activity of 5-(substituted) aryl-3-(3-coumarinyl)-1-phenyl-2- pyrazoline compounds.

Comp ID	100 mcg/ml	50 mcg/ml	25 mcg/ml	12.5 mcg/ml	6.25 mcg/ml	3.125 mcg/ml	1.6 mcg/ml	0.8 mcg/ml	0.4 mcg/ml	0.2 mcg/ml
A_1	S	S	S	S	S	S	S	R	R	R
A_2	S	S	S	S	R	R	R	R	R	R
A_3	S	S	S	S	S	S	S	R	R	R
A_4	S	S	S	S	S	S	S	S	R	R
A_5	S	S	S	S	S	S	R	R	R	R
A_6	S	S	S	S	S	S	S	R	R	R
Streptomycin	S	S	S	S	S	S	S	R	R	R

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REFERENCES

1. Ania, A. E.; Idokob, J.; Dalyopc, Y. B.; Pitmangd, S. L. T. Roy. Soci. Trup. Med. H., 2009; 103: 67.

2. Said, H. A.; Abdel, G. S.; Morlock, G.; Cooksey, R. C. Int. J. Infect. Dis., 2009; 13: 673.
3. Manjunath G, Manohar D, Kulkarni V, Shobha R, Kattimani SY. Synthesis of vanillin ethers from 4-(bromomethyl) coumarins as anti-in.ammatory agents. . *Eur J Med Chem*, 2003; 38: 297-302.
4. Christos AK, Dimitra JH. Synthesis and biological evaluation of novel coumarin derivatives with a 7-azomethine linkage. *Bioorg Med Chem Lett*, 2004; 14: 611-4.
5. Imtyaz A, Manohar V K, Gopal M, Shahabuddinb MS, Chung-Ming S. Synthesis and biological evaluation of novel angularly fused polycyclic coumarins. *Bioorg Med Chem Lett*, 2005; 15: 3584-7.
6. Fabrice B, Cedric M, Elisabeth T, Herve V, Philippe C. Antioxidant properties of 3-hydroxycoumarin derivatives. *Bioorg Med Chem Lett*, 2004; 12: 5611-8.
7. Vassiliki P, Ioannis K, Panagiotis M, Nicole P, Ioanna A. Synthesis and free radical scavenging activity of some new spiropyranocoumarins. *Bioorg Med Chem Lett*, 2008; 18: 5781-4.
8. Stanchev S, Hadjimitova V, Traykov T, Boyanov T, Manolov I. Investigation of the antioxidant properties of some new 4-hydroxycoumarin derivatives. *Eur J Med Chem*, 2009; 44: 3077-82.
9. Theodoros S, Michael C, Dimitra JH, Michael K, Konstantinos EL. Synthesis of hydroxycoumarins and hydroxybenzo[*f*]-or [*h*] coumarins as lipid peroxidation inhibitors. *Eur J Med Chem*, 2009; 19: 1139-42.
10. George K, Vassiliki T, Chryssa T. Synthesis and *in vitro* cytotoxicity of aminocoumarin platinum (II) complexes. Synthesis and *in vitro* cytotoxicity of aminocoumarin platinum (II) complexes. *Bioorg Med Chem Lett*, 1997; 7: 2165- 68.
11. Irena K, Ilia M, Irina N, Spiro K, Margarita K. New lanthanide complexes of 4-methyl-7-hydroxycoumarin and their pharmacological activity. *Eur J Med Chem*, 2001; 36: 339-47.
12. Natala SR, Muralidhar R, Stephen C, Kiranmai G, Stanley CB, Premkumar R. Synthesis of new coumarin 3-(N-aryl) sulphonamides and their anticancer activity. *Bioorg Med Chem Lett*, 2004; 14: 4093-7.
13. Irena K, Momekov G. New zirconium (IV) complexes of coumarins with cytotoxic activity. *Eur J Med Chem*, 2006; 41: 717-26.
14. Wei-wei M, Ting-ting W, He-ping Z, Zhi-yu W, Jian-ping C, Jian-gang S. Synthesis and evaluation of novel substituted 5-hydroxycoumarin and pyranocoumarin derivatives exhibiting signi.cant antiproliferative activity against breast cancer cell lines. *Bioorg Med Chem Lett*, 2009; 19: 4570-3.
15. Jeremiah JS, Ashley KW, Yousef RM, Michael DC, David EL. New adjuvants to enhance anticoagulant activity of Warfarin. *Bioorg Med Chem Lett*, 2010; 20: 1928-32.
16. Omaima MA, Kamelia MA, Rasha ZB, Timothy JM, Somaia AN, Shalini S. Synthesis, anticoagulant and PIVKA-II induced by new 4-hydroxy coumarin derivatives. *Bioorg Med Chem Lett*, 2010; 18: 3371-8.
17. Rangappa SK, Kallappa MH, Ramya VS, Mallinath HH. Analgesic, anti-pyretic and DNA cleavage studies of novel pyrimidine derivatives of coumarin moiety. *Eur J Med Chem*, 2010; 45: 2597-2605.
18. Ilia M, Danchev ND. Synthesis, toxicological and pharmacological assessment of some 4-hydroxycoumarin derivatives. *Eur J Med Chem*, 1995; 30: 531-5.
19. Ilia M, Caecilia M, Nicolay D. Synthesis, structure, toxicological and pharmacological investigations of 4-hydroxycoumarin derivatives. *Eur J Med Chem*, 2006; 41: 882-90.