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Synthesis and anti-inflammatory activities of 7-Benzylidene-2, 3-diphenyl-4, 5, 6, 7-tetrahydro-2H-indazole derivatives

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ABSTRACT

7-Benzylidene-2, 3-diphenyl-4, 5, 6, 7-tetrahydro-2H-indazole derivatives (7a-7k) have been prepared by cyclocondensation between different dibenzylidine cyclohexanones and phenyl hydrazine using absolute ethanol and pyridine. Dibenzylidine cyclohexanones are prepared from claisen condensation of appropriate aldehydes (alkyl, alkoxy and halo aromatic aldehydes) and cyclohexanones (cyclohexanone and methyl cyclohexanone).Structures of the compounds (1a-k, 2a-k and 3a-k) are confirmed using IR, NMR and Mass spectral details).The title compounds have been tested for their anti-inflammatory activity.

Keywords: indazoles, anti-inflammatory, diphenyl

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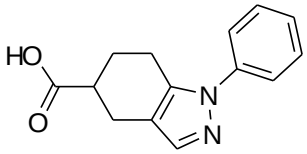
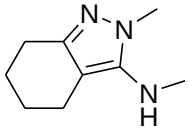
INTRODUCTION

The non-steroidal anti-inflammatory drugs (NSAIDs) are widely used for the treatment of minor pain, inflammation and for the management of edema and tissue damage resulting from inflammatory joint disease (arthritis). Design, synthesis and evaluation of NSAIDs continues to be a major area of activity, because, despite the progress made in this area, complete control of associated disorders with drugs of least side-effect is still a distinct dream. Till today, a number of sub-classes had been introduced including salicylates, propionic acids (profens), aryl and heteroaryl acetic acids, anthranilates (fenamates), oxicams ("enol acids"), phenylpyrazolones, anilides and so on. As part of our ongoing program of random screening to search for new pharmacophores, 4, 5, 6, 7-Tetrahydro-1H-indazoles have also been introduced as a new class of anti-inflammatory agents.

Interest in 4,5,6,7-Tetrahydro-1H-indazoles chemistry is unabated because of their useful biological activities such as antitumor [1], antimicrobial [2], nitric oxide synthase inhibitory [3], dopaminergic [4], HMG-CoA reductase inhibitory [5], cholesterol lowering [6], mitotic motor protein modulatory [7] and Rho-kinase inhibitory [8] . Working on the same line Nagakura M. et. al. had synthesized series of anti-inflammatory 1-aryl-4,5,6,7-tetrahydro-1H-indazole-5-carboxylic acids out of which 1-phenyl-4,5,6,7-tetrahydro-1H-indazole-5-carboxylic acid (**1**) being the most active with ED50 value of 3.5 mg/kg [9]. Scuri R. had reported analgesic and anti-inflammatory activity of 2-methyl-3-methylamino-4,5,6,7-tetrahydroindazole (**2**) [10].



(1)



(2)

The prevalent method of synthesis of tetrahydroindazole moieties involve refluxing of cyclohexanone derivatives with corresponding hydrazine at about 80^{o}C for 4 to 6 hours in alcohol. Catti F. et. al. had reported 'Green method' to synthesis similar compounds with microwave heating (200 W) for 25 min at 65°C [11].

EXPERIMENTAL

Melting points of the synthesized compounds were determined in open capillary tubes and were uncorrected. ^{1}H NMR spectra were recorded on a Bruker (400 MHz) using $CDCl_3$ / DMSO as solvents with tetramethylsilane (TMS) as internal standard. The structures of the compounds were established on the basis of elemental analysis and spectral data.

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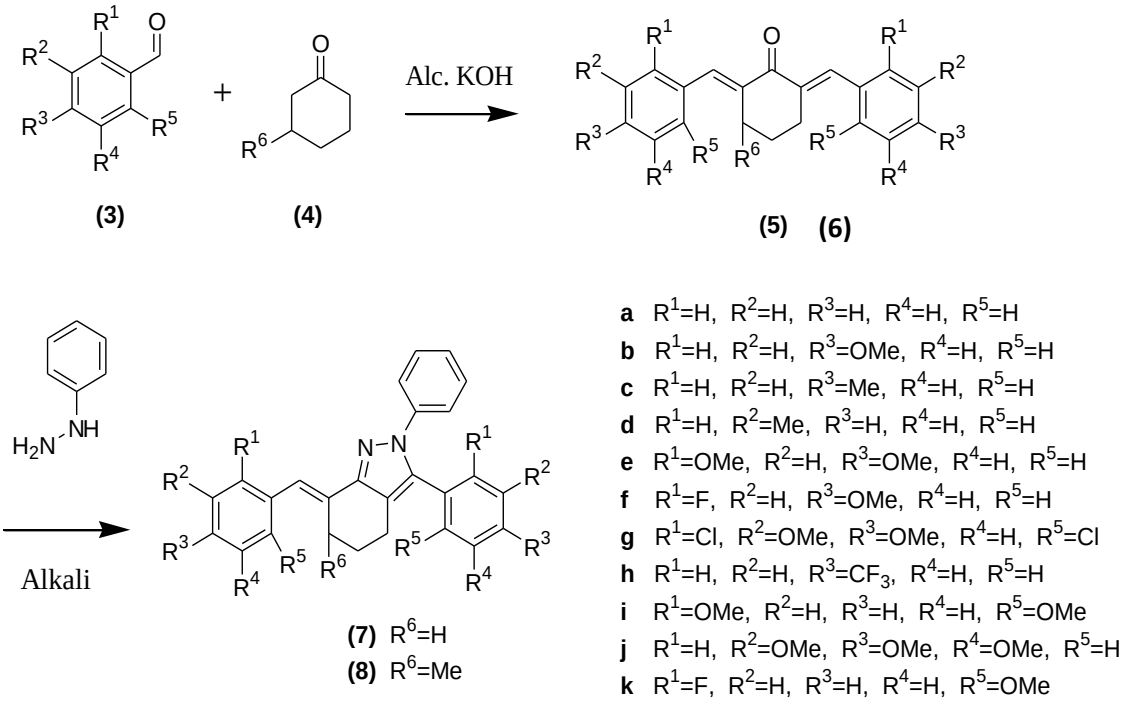

Scheme-1

General procedure for the synthesis of dibenzylidine cyclohexanone(bis chalcones) from cyclohexanone and 3-methyl cyclohexanone

A mixture of 30ml of 10% NaOH (ethanolic), 50ml of ethanol and 0.01 mole of cyclohexanone were placed in a 250 ml round bottomed flask, which was immersed in an ice bath as well as equipped with mechanical stirrer. The mixture was stirred for 10 minutes. 0.02 mole of aldehyde dissolved in ethanol was added to the mixture dropwise using addition funnel. The solution was stirred for 4hrs at RT. Then, to the mixture ice cold water was added and was neutralized with dilHCl. The resulting solid was filtered, washed with water and dried. Then it was washed with hexane (2 to 5 times) and it was purified by recrystallisation or column chromatography using hexane and ethylacetate as solvent mixture.

General procedure for the synthesis of 7-Benzylidene-2, 3-diphenyl-4, 5, 6, 7-tetrahydro-2H-indazole derivatives (7a-7k)

Indazole derivatives have been prepared by refluxing different dibenzylidine cyclohexanones and phenyl hydrazine using absolute ethanol and pyridine for three hours and purifying the reaction mixture either by column chromatograpy or recrystallisation.

2, 6 dibenzylidine cyclohexanone: (5a)

m.p.172^{o} C, ^{1}H NMR 1.68(2H, m, -CH_2-) 2.88(4H, m, -CH_2-) 7.37(2H, m, aromatic)7.46 (4H, m, aromatic) 7.52 (4H , m , aromatic) 7.62 (2H,s,=CH-).

2, 6 di (4', 4" dimethoxy) benzylidine cyclohexanone: (5b)

m.p.160^{o} C, ^{1}H NMR 1.76(2H, m, -CH_2-) 2.89(4H, m, -CH_2-) 3.83(6H, m, Ar-OCH_3) 6.91 (4H, m, aromatic) 7.45 (4H , m , aromatic) 7.75 (2H,s,=CH-)

2, 6 di (4', 4" dimethyl) benzylidine cyclohexanone: (5c)

m.p.167^{o} C, ^{1} H NMR 1.78(2H, m, -CH_2-) 2.37(6H, -CH_3) 2.9 (4H,m,-CH_2-) 7.25(4H, m, aromatic)7.38 (4H, m, aromatic) 7.76 (2H , s , =CH-)

2, 6 di (3', 3" dimethyl) benzylidine cyclohexanone: (5d)

m.p.120^{o} C, ^{1} H NMR 1.75(2H, m, -CH_2-) 2.38(6H, -CH_3) 2.9 (4H,m,-CH_2-) 7.29(4H, m, aromatic)7.38 (4H, m, aromatic) 7.76 (2H , s , =CH-)

2, 6 di (2', 4'& 2", 4" tetramethoxy) benzylidine cyclohexanone: (5e)

m.p.180^{o} C, ^{1}H NMR 1.60(2H, m, -CH_2-) 2.84(4H, -CH_2-) 3.83 (12H,s,-aromaticOCH_3-) 6.5 (4H, m, aromatic)7.28 (2H, m, aromatic) 7.95 (2H , s , =CH-)

2, 6 di (2', 2" difluoro 4',4" dimethoxy) benzylidine cyclohexanone: (5f)

m.p.160^{o} C, ^{1}H NMR 1.76(2H, m, -CH_2-) 2.81(4H, m, -CH_2-) 3.83(6H, m, Ar-OCH_3) 6.65 (2H,dd, aromatic) 6.73 (2H ,dd , aromatic) 7.33 (2H,t,aromatic) 7.81(2H,s,=CH)

2, 6 di (2'6', 2"6"tetrachloro 3,3", 4',4" dimethoxy) benzylidine cyclohexanone: (5g)

m.p.150^{o} C, ^{1}H NMR 1.72(2H, m, -CH_2-) 2.45(4H, m, -CH_2-) 3.85(3H, m, Ar-OCH_3)3.88(3H,m,Ar-OCH_3)6.92 (2H,dd, aromatic)7.52(2H,s,=CH)

2, 6 di (4', 4" di (α,α,α triflouromethyl) benzylidine cyclohexanone: (5h)

m.p.167^{o} C, ^{1}H NMR 1.78(2H, m, -CH_2-) 2.9 (4H,m,-CH_2-) 7.25(4H, m, aromatic)7.38 (4H, m, aromatic) 7.76 (2H , s , =CH-)

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2, 6 di (2', 6'& 2", 6" tetramethoxy) benzylidine cyclohexanone: (5i)

m.p.178^{o}C, ^{1}H NMR 1.70(2H, m, -CH_2-) 2.81(4H, -CH_2-) 3.83 (12H,s,-aromaticOCH_3-) 6.5 (4H, m, aromatic)7.24 (2H, m, aromatic) 7.85 (2H , s , =CH-)

2, 6 di (3, 3', 4', 4", 5', 5" hexamethoxy) dibenzylidine cyclohexanone: (5j)

m.p.89^{o}C, ^{1}H NMR 1.84(1H, m, -CH-) 1.90 (1H,m,-CH_2 -) 2.99 (2H,m,-CH_2-), 3.48(2H, m, -CH_2-) 3.4(18H, m,-CH_3O-)6.72(4H, m, aromatic)7.58(1H, s,=CH-) 7.69 (1H,s,=CH-)

2, 6 di (2', 2" difluoro 6',6" dimethoxy) benzylidine cyclohexanone: (5k)

m.p.160^{o}C, ^{1}H NMR 1.74(2H, m, -CH_2-) 2.75(4H, m, -CH_2-) 3.82(6H, m, Ar-OCH_3) 6.70 (2H,dd, aromatic) 6.73 (2H ,dd , aromatic) 7.33 (2H,m,aromatic) 7.81(2H,s,=CH)

2, 6 dibenzylidine 3 methylcyclohexanone: (6a)

m.p.82^{o}C, ^{1}H NMR 1.30(3H, d, CH_3)1.79(1H, m, -CH_2-)1.87(1H,m,-CH_2 -) 2.97(2H, m, -CH_2-) 3.47(1H,m,-CH-)7.31(2H, m, aromatic)7.41(4H, m, aromatic) 7.48 (4H , m , aromatic) 7.64 (1H,s,=CH-),7.65 (1H,s,=CH-)

2, 6 (4', 4" dimethoxy) dibenzylidine 3 methylcyclohexanone: (6b)

m.p.108^{o}C, ^{1}H NMR 1.05(3H, d, CH_3)1.37 (1H, m, -CH-) 1.90 (1H,m,-CH_2 -) 2.09 (1H,m,-CH_2-), 2.62(2H, m, -CH_2-) 3.84(6H, m,-CH_3O-) 6.92(4H, m, aromatic)7.41(4H, m, aromatic) 7.48 (2H,s,=CH-)

2, 6 (4', 4" dimethyl) dibenzylidine 3 methylcyclohexanone: (6c)

m.p.128^{o}C, ^{1}H NMR 1.31(3H, d, CH_3)1.79 (1H, m, -CH_2-) 1.87 (1H,m,-CH_2 -) 2.38 (6H,aromatic methyl), 2.97(2H, m, -CH_2-) 3.48(1H,m,-CH-)7.19 (4H, m, aromatic)7.41(4H, m, aromatic) 7.62 (1H,s,=CH-),7.73 (1H,s,=CH-)

2, 6 di (2', 4'& 2", 4" tetramethoxy) benzylidine 3-methyl cyclohexanone: (6e)

m.p.145^{o}C, ^{1}H NMR 1.31(3H, d, CH_3)1.62(1H, m, -CH_2-) 1.84(1H, m, -CH-) 2.85(4H, -CH_2-) 3.81 (12H,s,-aromaticOCH_3-) 6.49(4H, m, aromatic)7.30 (2H, m, aromatic) 7.93 (2H , s , =CH-)

2, 6 di (2', 2" difluoro 4', 4" dimethoxy) benzylidine 3-methyl cyclohexanone: (6f)

m.p.130^{o}C, ^{1}H NMR 1.25(3H,d,CH_3) 1.76(2H, m, -CH_2-) 2.81(4H, m, -CH_2-) 3.83(6H, m, Ar-OCH_3) 6.65 (2H,dd, aromatic) 6.73 (2H ,dd , aromatic) 7.33 (1H,t,aromatic) 7.81(2H,s,=CH)

2, 6 di (2'6', 2"6"tetrachloro 3, 3", 4', 4" dimethoxy) benzylidine 3-methylcyclohexanone: (6g)

m.p.140^{o} C, ^{1}H NMR 1.28 (3H,s,CH_3)1.72(2H, m, -CH_2-) 2.45(4H, m, -CH_2-) 3.85(3H, m, Ar-OCH_3)3.88(3H,m,Ar-OCH_3)6.92 (2H,dd, aromatic) 7.52(2H,s,=CH)

2, 6 di (4', 4" di (α,α,α triflouromethyl) benzylidine 3-methylcyclohexanone: (6h)

m.p.162^{o} C, ^{1}H NMR 1.34(3H,d,CH_3)1.78(2H, m, -CH_2-) 2.9 (4H,m,-CH_2-) 7.25(4H, m, aromatic)7.38 (4H, m, aromatic) 7.76 (2H , s , =CH-)

2, 6 di (2', 6'& 2", 6" tetramethoxy) benzylidine 3-methylcyclohexanone: (6i)

m.p.178^{o} C, ^{1}H NMR1.35 (3H,d,CH_3)1.70(2H, m, -CH_2-) 2.81(4H, -CH_2-) 3.83 (12H,s,-aromaticOCH_3-) 6.5 (4H, m, aromatic)7.24 (2H, m, aromatic) 7.85 (2H , s , =CH-)

2, 6 (3, 3', 4', 4", 5', 5" hexamethoxy) dibenzylidine 3methyl cyclohexanone: (6j)

m.p.95^{o} C, ^{1}H NMR 1.35(3H, d, CH_3)1.84(1H, m, -CH-) 1.90 (1H,m,-CH_2 -) 2.99 (2H,m,-CH_2 -), 3.45(1H, m, -CH_2-) 3.4(18H, m,-CH_3O-)6.72(4H, m, aromatic)7.58(1H, s,=CH-) 7.69 (1H,s,=CH-)

2, 6 di (2',2" difluoro 6',6" dimethoxy) benzylidine 3-methylcyclohexanone: (6k)

m.p.163^{o} C, ^{1}H NMR1.30(3H, d, CH_3) 1.74(2H, m, -CH_2-) 2.75(4H, m, -CH_2-) 3.82(6H, m, Ar-OCH_3) 6.70 (2H,dd, aromatic) 6.73 (2H ,dd , aromatic) 7.33 (1H,t,aromatic) 7.81(2H,s,=CH)

7-Benzylidene-2, 3-diphenyl-4, 5, 6, 7-tetrahydro-2H-indazole (7a)

m.p.242^{o} C, ^{1}H NMR 1.69(2H, m, -CH_2-) 2.98(4H, m, -CH_2-) 7.37(2H, m, aromatic) 7.46 (4H, m, aromatic) 7.5 (3H, aromatic) 7.52 (6H , m , aromatic) 7.62 (1H,s,=CH-)

7-(4'-methoxy) benzylidene-2 phenyl 3-(4''-methoxy) phenyl-4, 5, 6, 7-tetrahydro-2H-indazole (7b)

m.p.260^{o} C, ^{1}H NMR 1.70(2H, m, -CH_2-) 2.87(4H, m, -CH_2-) 3.81(6H, m, Ar-OCH_3) 6.90 (4H, m, aromatic) 7.45 (9H , m , aromatic) 7.75 (1H,s,=CH-)

7-(4'-methyl) benzylidene-2-phenyl 3-(4'' methyl) phenyl-4, 5, 6, 7-tetrahydro-2H-indazole (7c)

m.p.267^{o} C, ^{1}H NMR 1.79(2H, m, -CH_2-) 2.27(6H, -CH_3) 2.95 (4H,m,-CH_2-) 7.25(6H, m, aromatic)7.40 (7H, m, aromatic) 7.76 (1H , s , =CH-)

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7-(3'-methyl) benzylidene-2-phenyl 3-(3'' methyl) phenyl-4, 5, 6, 7-tetrahydro-2H-indazole (7d)

m.p.260^{o} C, ^{1} H NMR 1.79(2H, m, -CH_2-) 2.32(6H, -CH_3) 2.90 (4H,m,-CH_2-) 7.29(6H, m, aromatic)7.38 (7H, m, aromatic) 7.76 (1H , s , =CH-)

7-(2', 4'-dimethoxy) benzylidene-2-phenyl 3-(2'', 4'' dimethoxy) phenyl-4, 5, 6, 7-tetrahydro-2H-indazole (7e)

m.p.254^{o} C, ^{1} H NMR 1.60(2H, m, -CH_2-) 2.84(4H, -CH_2-) 3.83 (12H,s,-aromatic OCH_3-) 6.5 (6H, m, aromatic)7.28 (5H, m, aromatic) 7.95 (1H , s , =CH-)

7-(2'-fluoro 4'-methoxy) benzylidene-2-phenyl 3-(2''-fluoro 4''-methoxy) phenyl-4, 5, 6, 7-tetrahydro-2H-indazole (7f)

m.p.261^{o} C, ^{1} H NMR 1.76(2H, m, -CH_2-) 2.81(4H, m, -CH_2-) 3.83(6H, m, Ar-OCH_3) 6.65 (3H,dd, aromatic) 6.73 (4H ,dd , aromatic) 7.33 (4H,t,aromatic) 7.81(1H,s,=CH)

7-(2', 6'-dichloro 3', 4'-dimethoxy) benzylidene-2-phenyl 3-(2'', 6''-dichloro 3'', 4''-dimethoxy)phenyl-4, 5, 6, 7-tetrahydro-2H-indazole (7g)

m.p.249^{o} C, ^{1} H NMR 1.78(2H, m, -CH_2-) 2.9 (4H,m,-CH_2-) 7.25(4H, m, aromatic)7.38 (3H, m, aromatic) 7.76 (1H , s , =CH-)

7-(4'-trifluoro methyl) benzylidene-2 phenyl 3-(4''-trifluoro methyl) phenyl-4, 5, 6, 7-tetrahydro-2H-indazole (7h)

m.p.267^{o} C, ^{1} H NMR 1.70(2H, m, -CH_2-) 2.85 (4H,m,-CH_2-) 7.32(4H, m, aromatic)7.38 (4H, m, aromatic) 7.54(5H, m, aromatic)7.76 (1H , s , =CH-)

7-(2', 6'-dimethoxy) benzylidene-2 phenyl 3-(2', 6'-dimethoxy) phenyl-4, 5, 6, 7-tetrahydro-2H-indazole (7i)

m.p.248^{o} C, ^{1} H NMR 1.70(2H, m, -CH_2-) 2.91(4H, -CH_2-) 3.73 (12H,s,-aromaticOCH_3-) 6.5 (7H, m, aromatic)7.24 (4H, m, aromatic) 7.85 (1H , s , =CH-)

7-(3', 4', 5'-trimethoxy) benzylidene-2 phenyl 3-(3'', 4'', 5''-trimethoxy) phenyl-4, 5, 6, 7-tetrahydro-2H-indazole (7j)

m.p.189^{o} C, ^{1} H NMR 1.84(1H, m, -CH-) 1.90 (1H,m,-CH_2 -) 2.99 (2H,m,-CH_2 -), 3.48(1H, m, -CH_2-) 3.4(18H, m,-CH_3O-)6.72(4H, m, aromatic)7.34(5H,m,aromatic)7.69 (1H,s,=CH-)

7-(2' fluoro-6'methoxy) benzylidene-2 phenyl 3-(2' fluoro-6'methoxy) phenyl-4, 5, 6, 7-tetrahydro-2H-indazole (7k)

m.p.230^{o}C, ^{1}H NMR 1.74(2H, m, -CH_2-) 2.75(4H, m, -CH_2-) 3.82(6H, m, Ar-OCH_3) 6.70 (2H,dd, aromatic) 6.73 (4H ,dd , aromatic) 7.33 (5H,t,aromatic) 7.81(1H,s,=CH)

7-Benzylidene-2, 3-diphenyl-6-methyl -4, 5, 6, 7-tetrahydro-2H-indazole (8a)

m.p. 212^{o}C, ^{1}H NMR 1.31(3H, d, CH_3)1.62(1H, m, -CH_2-) 1.69(2H, m, -CH_2-) 2.98(2H, m, -CH_2-) 7.30(2H, m, aromatic) 7.41(4H, m, aromatic) 7.49(3H, aromatic) 7.52 (6H , m , aromatic) 7.62 (1H,s,=CH-)

7-(4'-methoxy) benzylidene-2 phenyl 3-(4''-methoxy) phenyl-6-methyl -4, 5, 6, 7-tetrahydro-2H-indazole (8b)

m.p.210^{o}C, ^{1}H NMR1.27(3H, d, CH_3)1.62(1H, m, -CH_2-) 1.70(1H, m, -CH_2-) 2.87(3H, m, -CH_2-) 3.81(6H, m, Ar-OCH_3) 6.95(4H, m, aromatic) 7.47(9H , m , aromatic) 7.75 (1H,s,=CH-)

7-(4'-methyl) benzylidene-2-phenyl 3-(4'' methyl) phenyl-6-methyl -4, 5, 6, 7-tetrahydro-2H-indazole (8c)

m.p.227^{o}C, ^{1}H NMR1.39(3H, d, CH_3)1.62(1H, m, -CH_2-) 1.79(2H, m, -CH_2-) 2.27(6H, -CH_3) 2.95 (2H,m,-CH_2-) 7.29(6H, m, aromatic)7.40 (7H, m, aromatic) 7.73 (1H , s , =CH-)

7-(3'-methyl) benzylidene-2-phenyl 3-(3'' methyl) phenyl-6-methyl -4, 5, 6, 7-tetrahydro-2H-indazole (8d)

m.p.210^{o}C, ^{1}H NMR 1.30(3H, d, CH_3)1.62(1H, m, -CH_2-) 1.79(2H, m, -CH_2-) 2.32(6H, -CH_3) 2.80 (2H,m,-CH_2-) 7.26(6H, m, aromatic)7.38 (7H, m, aromatic) 7.76 (1H , s , =CH-)

7-(2', 4'-dimethoxy) benzylidene-2-phenyl 3-(2'', 4'' dimethoxy) phenyl-6-methyl -4, 5, 6, 7-tetrahydro-2H-indazole (8e)

m.p.214^{o}C, ^{1}H NMR 1.21(3H, d, CH_3)1.69(1H, m, -CH_2-) 1.60(2H, m, -CH_2-) 2.84(2H, -CH_2-) 3.83 (12H,s,-aromatic OCH_3-) 6.57(6H, m, aromatic)7.22 (5H, m, aromatic) 7.95 (1H , s , =CH-)

7-(2'-fluoro 4'-methoxy) benzylidene-2-phenyl 3-(2''-fluoro 4''-methoxy) phenyl-6-methyl -4, 5, 6, 7-tetrahydro-2H-indazole (8f)

m.p.211^{o}C, ^{1}H NMR 1.31(3H, d, CH_3)1.61(1H, m, -CH_2-) 1.76(2H, m, -CH_2-) 2.71(2H, m, -CH_2-) 3.83(6H, m, Ar-OCH_3) 6.65 (3H,dd, aromatic) 6.93 (4H ,dd , aromatic) 7.43 (4H,t,aromatic) 7.81(1H,s,=CH)

7-(2',6'-dichloro 3', 4'-dimethoxy) benzylidene-2-phenyl 3-(2'',6''-dichloro 3'', 4''-dimethoxy)phenyl-6-methyl -4, 5, 6, 7-tetrahydro-2H-indazole (8g)

m.p.209^{o} C, ^{1}H NMR 1.31(3H, d, CH_3)1.52(1H, m, -CH_2-) 1.78(2H, m, -CH_2-) 2.9 (2H,m,-CH_2-) 7.20(4H, m, aromatic)7.38 (3H, m, aromatic) 7.86 (1H , s , =CH-)

7-(4'-trifluoro methyl) benzylidene-2 phenyl 3-(4''-trifluoro methyl) phenyl-6-methyl -4, 5, 6, 7-tetrahydro-2H-indazole (8h)

m.p.217^{o} C, ^{1}H NMR1.29(3H, d, CH_3)1.42(1H, m, -CH_2-) 1.70(2H, m, -CH_2-) 2.75 (2H,m,-CH_2-) 7.32(4H, m, aromatic)7.38 (4H, m, aromatic) 7.54(5H, m, aromatic)7.76 (1H , s , =CH-)

7-(2', 6'-dimethoxy) benzylidene-2 phenyl 3-(2', 6'-dimethoxy) phenyl-6-methyl 4, 5, 6, 7-tetrahydro-2H-indazole (8i)

m.p.228^{o} C, ^{1}H NMR 1.21(3H, d, CH_3)1.42(1H, m, -CH_2-) 1.70(2H, m, -CH_2-) 2.91(2H, -CH_2-) 3.73 (12H,s,-aromatic OCH_3-) 6.59(7H, m, aromatic)7.24 (4H, m, aromatic) 7.85 (1H , s , =CH-)

7-(3', 4', 5'-trimethoxy) benzylidene-2 phenyl 3-(3', 4', 5'-trimethoxy) phenyl-6-methyl -4, 5, 6, 7-tetrahydro-2H-indazole (8j)

m.p.198^{o} C,^{1}H NMR1.25(3H, d, CH_3)1.42(1H, m, -CH_2-)1.84(1H, m, -CH-) 1.90 (1H,m,-CH_2 -) 2.99 (2H,m,-CH_2 -) 3.4(18H, m,-CH_3O-)6.72(4H, m, aromatic)7.34(5H,m,aromatic)7.69 (1H,s,=CH-)

7-(2' fluoro-6'methoxy) benzylidene-2 phenyl 3-(2' fluoro-6'methoxy) phenyl-6-methyl-4, 5, 6, 7-tetrahydro-2H-indazole (8k)

m.p.200^{o} C, ^{1}H NMR 1.32(3H, d, CH_3)1.52(1H, m, -CH_2-) 1.74(2H, m, -CH_2-) 2.75(2H, m, -CH_2-) 3.82(6H, m, Ar-OCH_3) 6.67 (2H,dd, aromatic) 6.73 (4H ,dd , aromatic) 7.33 (5H,t,aromatic) 7.80(1H,s,=CH)

The synthesized derivatives were evaluated for *In vivo* antiinflammatory assay methods.

Antiinflammatory activity

Carrageenan-induced paw edema in rats

All the synthesized compounds (**7a-k** and **8a-k**) were tested for their anti-inflammatory activity against carrageenan-induced edema at dose of 10 mg/kg using Indomethacin as reference standard. The percentage protection against inflammation was calculated using the formula given below:

$$(Vc - Vt) \div Vc \times 100$$

Where, Vc is the increase in paw volume of control (in the absence of test compound) and Vt is the increase in paw volume after administration of the test compound.

Protocol

Albino rats (both male and female) weighing between 150-210 g and were used in the present study. Animals were kept in wire-mesh cages and maintained under constant environmental conditions [23±2°C, 12hr, light]. All animal groups were under fasting for overnight and watered. During the course of experiment, the general behavior of animal was normal. All the experimental protocols were approved by the Institutional Animal Ethical Committee (IACE) and experiments were conducted in accordance with the standard guidelines.

The given data is of five animals per group and divided in to twenty three groups. Group-1 referred as control (animals received carrageenan along with the vehicle [0.5% carboxymethylcellulose (CMC)]. Group-2 to 23 received the test compounds (**7a-k and 8a-k**) respectively along with vehicle 1 hr prior to the administration of carrageenan and Group-26 received standard reference (aceclofenac 2 mg/kg) along with the vehicle prior to the administration of carrageenan. All the test compounds were suspended in 0.5% of CMC and administered orally (10 mg/kg) 60 min prior to the injection of 0.1 ml of freshly prepared carrageenan (1%) in physiological solution (100 mg carrageenan powder in 10 ml 0.9% NaCl set aside to soak for 1 hr and then homogenized with magnetic stirrer) into the sub-planter tissue of hind paw of each rat. The equivalent volume of carrageenan (1%) in physiological solution was injected into hind paw of the control. The thickness of both paws of each rat, lower and upper surface were measured using Zeitlin's constant load lever consisting of a graduated Micrometer combined with a constant loaded lever system to magnify the small changes in paw thickness during the course of experiment. The paw thickness was measured prior to the administration of carrageenan, 0.5, 1, 2, 3, 4 and 6 hrs after the injection. The increase in volume of the paw was adopted as a measure of edema. The anti-oedematous effects of the compounds were estimated as percentage inhibition in paw thickness in comparison with the control (Table).

CONCLUSION

As we expected, the pharmacophore 4, 5, 6, 7-Tetrahydro-1H-indazole exhibited anti-inflammatory activity with different substituents in different percentages. Out of all compounds 7g,7h,7i,8g,8h exhibited more activity. So with further work on this pharmacophore more promising compounds with excellent anti-inflammatory activity can be synthesized in the future.

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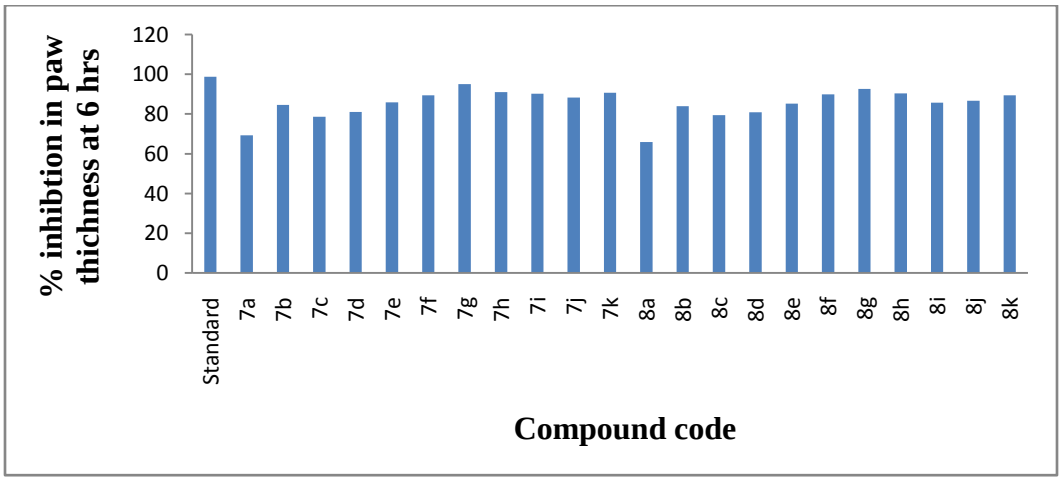
Compound code	% inhibtion in paw thickness at various time intervals					
	0.5 hr	1 hr	2 hr	3 hr	4 hr	6 hr
Standard	20.26±0.65	23.95±0.66	58.08±1.83	67.89±1.63	97.12±1.96	98.76±1.96
7a	12.99±0.47	20.19±0.61	27.72±0.79	50.73±2.36	67.25±1.62	69.34±1.63
7b	28.46±3.55	48.32±3.68	56.30±0.84	66.75±2.22	76.99±1.43	84.50±1.69
7c	15.93±0.89	29.34±0.93	57.65±3.02	66.78±1.49	71.39±1.41	78.65±1.91
7d	16.59±0.67	30.01±0.72	47.64±2.92	65.19±1.72	75.15±1.23	80.97±1.70
7e	39.42±2.26	47.37±2.54	49.97±1.24	57.47±3.65	78.27±1.68	85.90±1.82
7f	19.00±1.06	40.66±1.33	53.96±3.81	73.30±1.63	84.47±2.93	89.43±1.89
7g	21.86±0.83	34.21±1.67	69.48±2.36	80.02±2.38	89.05±1.33	**94.99±1.23**
7h	49.53±1.43	59.81±3.69	76.82±1.78	84.55±1.61	88.92±1.97	**91.04±1.72**
7i	32.33±2.65	44.59±2.79	56.41±1.83	69.86±3.22	78.27±1.90	**90.18±1.91**
7j	17.81±0.39	38.95±1.72	53.71±3.14	71.26±1.72	83.64±2.24	88.23±1.58
7k	18.71±0.56	39.26±1.60	57.64±2.25	78.47±1.96	82.94±2.61	90.76±1.47
8a	14.18±0.41	20.62±0.65	29.96±0.78	52.61±2.43	61.11±1.67	65.93±1.75
8b	28.2±3.64	47.12±4.23	56.31±0.98	66.19±2.32	78.01±1.66	83.97±1.88
8c	16.51±0.82	29.14±0.77	54.87±3.18	64.98±1.63	70.82±1.22	79.45±1.87
8d	15.59±0.67	30.07±0.72	49.75±2.99	65.28±1.54	73.31±1.19	80.92±1.64
8e	35.12±2.81	41.06±2.73	45.63±1.58	56.11±3.80	71.91±1.78	85.19±1.79
8f	18.63±0.27	39.12±1.47	53.14±3.38	73.26±1.61	84.48±2.49	89.83±1.92
8g	21.60±0.81	32.60±1.53	67.54±2.07	79.73±2.17	87.33±1.64	**92.67±1.44**
8h	47.3±1.54	56.28±3.14	69.21±1.42	79.36±1.59	83.99±1.90	**90.31±1.51**
8i	31.23±2.72	43.62±2.61	49.64±1.59	59.41±3.47	72.33±1.83	85.64±1.82
8j	19.63±0.22	37.81±1.35	52.62±4.14	71.28±1.53	82.49±2.52	86.73±1.40
8k	18.74±0.27	36.67±1.16	56.34±4.37	76.13±1.68	82.53±2.15	89.46±1.38

All values are expressed as mean±SEM (n=5)



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