

A one-pot microwave assisted synthesis of ethyl 7,7-dimethyl-5-oxo-4-aryl-2-[(arylsulfonyl)methyl]-1,4,5,6,7,8-hexahydroquinoline-3-carboxylates under solvent-free condition and their selective cyclooxygenase (COX-1 & COX-2) inhibitor studies

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ABSTRACT

A four-component domino reaction of ethyl-3-oxo-4-(arylsulfonyl) butanoates, aromatic aldehydes, dimesone and ammonium acetate under microwave irradiation in solvent free condition furnished a library of novel ethyl 7,7-dimethyl-5-oxo-4-aryl-2-[(arylsulfonyl)methyl]-1,4,5,6,7,8-hexahydroquinoline-3-carboxylates. This method provides many superiority like simplicity, very high yield and environment friendly. The reaction proceed through the Hantzsch condensation reaction. The synthesized compounds were subjected to selective cyclooxygenase (COX-1 & COX-2) inhibitor evaluation studies.

INTRODUCTION

In modern synthetic organic chemistry multi-component reactions (MCR) have been proved as a powerful and effective method of creation of several new bonds through one-pot synthesis. This includes two, three, four-component reactions for the synthesis of target compounds in a single step. This leads to the decrease in the reaction time, use of solvents and so on. Both in the academic and commercial sector, the practice of using MCR and domino sequences

to synthesise wide range of products have been emerging effectively.[1]

Compounds having quinolinone nucleus exhibit a complete range of pharmacological activities that makes the researchers to consider these compounds for drug evaluation. They are very popular as a pharmaceutical agents because they display wide range of properties such as antiproliferative,[2] antimicrobial,[3] anticancer, [4] antioxidant [5] and anti-tubercular [6] activities (**Figure 1**).

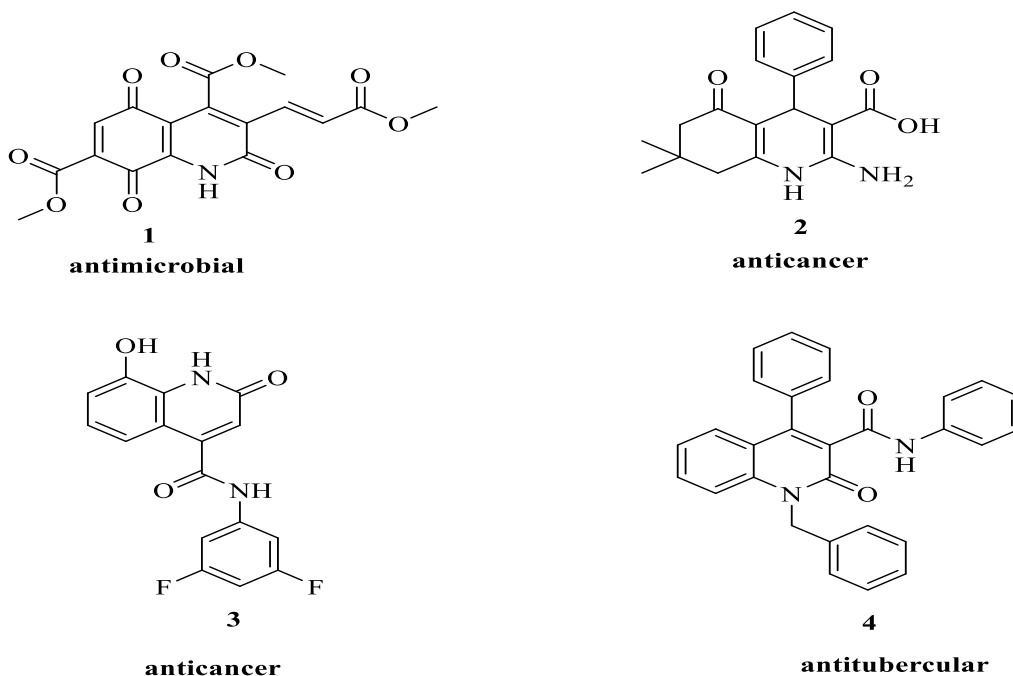


Figure 1. Quinoline derivative exhibiting biological activity

Calcium channel antagonist activity is shown by drugs like Lucidipine **5** and Nimodipine **6** are having 1,4-DHP nucleus and drugs like Nifedipine **7**, Amlopidine **8** and Nicardipine are act as a

cardiovascular agents and are used in the treatment of hypertension (**Figure 2**).

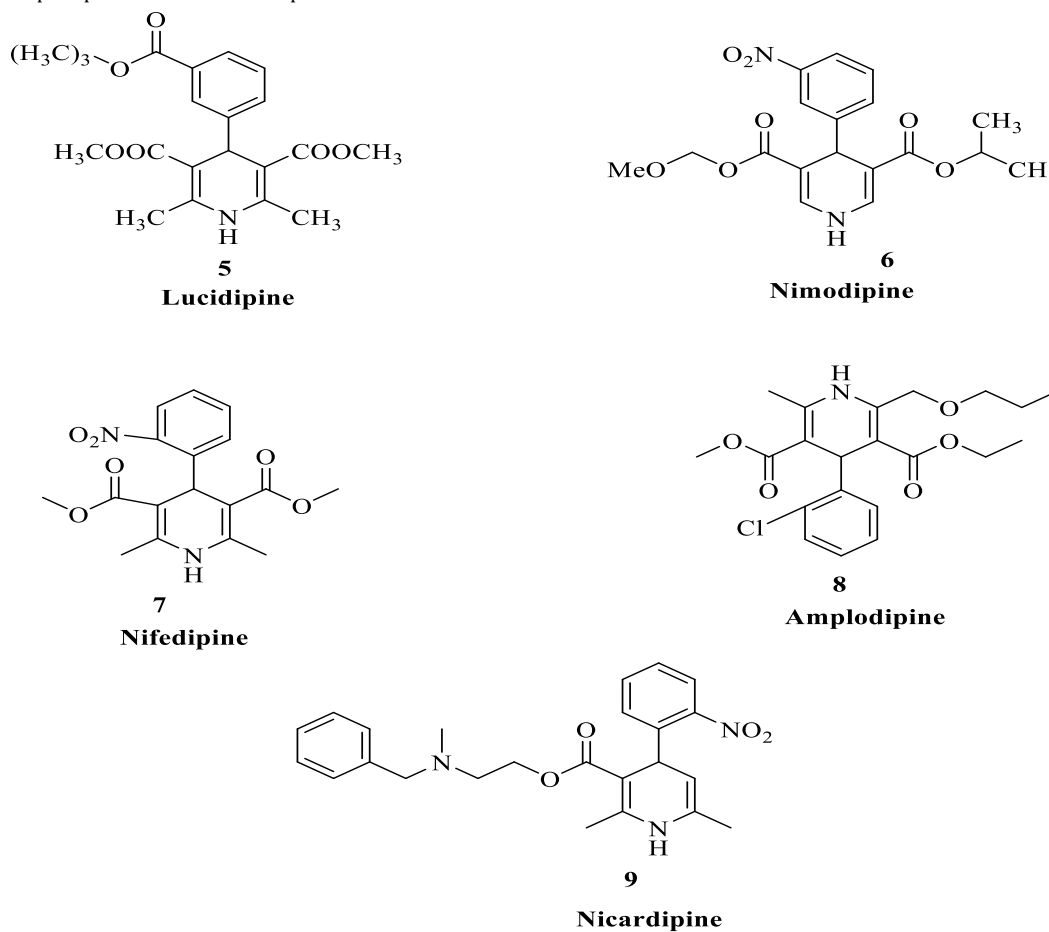
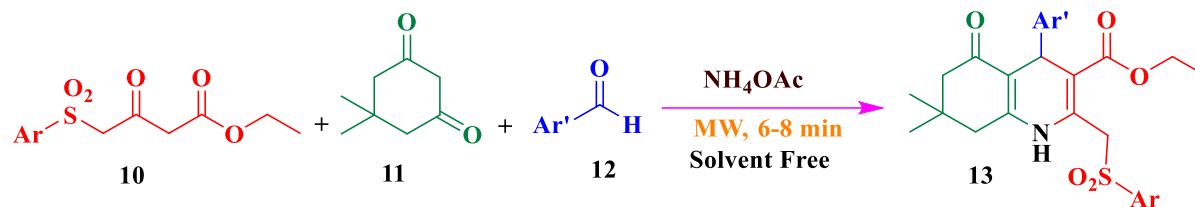


Figure 2. Drugs having 1,4-DHP unit

Besides this quinolones having 1,4-DHP nucleus are act as an effective pharmacological and therapeutic agents as antitumor, vasodilator, RESULTS & DISCUSSION:

geroprotective, bronchodilator, anti-inflammatory, anti-malarial, anti-bacterial and anti-asthmatic activities.[7]



Scheme 1. Synthesis of HHQ

In the Present work a one-pot microwave assisted synthesis of ethyl 7,7-dimethyl-5-oxo-4-aryl-2-[(arylsulfonyl)methyl]-1,4,5,6,7,8-hexahydroquinoline-3-carboxylates under solvent condition and their selective cyclooxygenase (COX-1 & COX-2) inhibitor studies. A mixture ethyl-3-oxo-4-(arylsulfonyl)butanoates **10** (1 mmol). Derivatives of aldehydes **12**, (1 mmol), ammonium acetate (1.2 mmol), along with dimedone **11** was taken in a 10 ml quartz vial, sealed and placed in a Biotage microwave oven. The vial was subjected to microwave irradiation, programmed at 120°C, 65 W, 2 bar pressure and very high absorption level for the required amount of period. After a period of 1-2 min., the temperature reached a plateau, 120 °C, and remained constant. After gas jet cooling to room temperature (3

min.), when the reaction ceases, the mixture was concentrated in vacuo to give the crude product. The crude product was purified by a short column chromatography on silica gel employing ethyl acetate-petroleum ether (1:4 v/v) as eluent to obtain pure product **13**.

The yield and reaction time was compared with the conventional thermal method (**Table 2**).

In the present investigation we have started our investigation by optimizing the reaction condition with respect to the solvent and catalyst (**Table 1**). The solvents, viz. CH₃CN, MeOH, EtOH, DMF and catalysts Cu(OAc)₂, AlCl₃, CH₃COOH, CeCl₃·7H₂O, SnCl₂, FeCl₃, were used for the optimize the reaction. Maximum yields were achieved when the reaction is performed without any solvent and catalyst.

Table 1 Catalyst and Solvent optimization for the synthesis of **13** under microwave irradiation.

Entry	Catalyst	Solvent	Time	Yield
1	Nil	Nil	10	88
2	Nil	EtOH	15	60
3	Nil	MeOH	15	58
4	Nil	DMF	20	40
5	Nil	CH ₃ CN	15	62
6	CH ₃ COOH	Nil	10	78
7	AlCl ₃	Nil	10	72
8	SnCl ₂	Nil	10	75
9	CeCl ₃ ·7H ₂ O	Nil	10	68
10	FeCl ₃	Nil	10	75
11	Cu(OAc) ₂	Nil	10	70

Besides this, under microwave irradiation for the synthesis of **13** was also performed at temp. ranging from 100 to 140 °C with an increment of 10 °C. Maximum yield of the product was attained when the temperature reaches 120°C and the completion of the reaction takes place within 8 minutes. As a result of this screening process all other reactions were achieved at 120°C without Catalyst- and Solvent. This method represents the first example of an efficient process for the synthesis of HHQ under solvent- and catalyst-free condition.

In addition, the reactions for synthesizing **13** were also performed under classical thermal method in ethanol under refluxing condition. The results reveal that the yield of the reaction under microwave irradiation is more, 74-93% than that under conventional heating conditions, 45-58% (**Table 2**). The reaction under microwave irradiation could also be completed more rapidly in minutes than under traditional heating conditions, *albeit* different temperatures were employed and the two protocols cannot be strictly compared.

Table 2 Synthesis of compound **13**
Comparison of Yield and reaction time between conventional and microwave-assisted reactions

Code	Ar	Ar'	Reaction time		Yield (%)		m.p (°C)
			Reflux ^a (80°C) (h)	MW ^b (120°C) (min)	Reflux ^c	MW	
13a	<i>p</i> -ClC ₆ H ₄	<i>p</i> -MeOC ₆ H ₄	3	6	45	88	212-213
13b	<i>p</i> -ClC ₆ H ₄	<i>p</i> -MeC ₆ H ₄	3	6	52	86	220-221
13c	<i>p</i> -ClC ₆ H ₄	<i>p</i> -ClC ₆ H ₄	3	8	48	90	218-220
13d	<i>p</i> -ClC ₆ H ₄	<i>p</i> -FC ₆ H ₄	3	8	55	80	224-225
13e	C ₆ H ₅	<i>p</i> -MeOC ₆ H ₄	3	8	45	93	220-221
13f	C ₆ H ₅	<i>p</i> -MeC ₆ H ₄	3	6	50	89	227-228
13g	C ₆ H ₅	<i>p</i> -ClC ₆ H ₄	3	8	58	78	203-204
13h	C ₆ H ₅	<i>p</i> -FC ₆ H ₄	3	8	52	91	207-208
13i	<i>p</i> -Me-C ₆ H ₄	<i>p</i> -MeOC ₆ H ₄	3	6	44	78	211-212
13j	<i>p</i> -Me-C ₆ H ₄	<i>p</i> -MeC ₆ H ₄	3	6	56	92	231-232
13k	<i>p</i> -Me-C ₆ H ₄	<i>p</i> -Cl-C ₆ H ₄	3	8	48	75	201-202
13l	<i>p</i> -Me-C ₆ H ₄	<i>p</i> -F-C ₆ H ₄	3	8	48	93	198-199
13m	<i>p</i> -Me-C ₆ H ₄	<i>o</i> -MeOC ₆ H ₄	3	6	56	86	219-220
13n	C ₆ H ₅	<i>o</i> -MeC ₆ H ₄	3	6	52	74	226-227
13o	C ₆ H ₅	<i>o</i> -Cl-C ₆ H ₄	3	8	56	85	230-231
13p	C ₆ H ₅	<i>o</i> -NO ₂ -C ₆ H ₄	3	8	45	92	198-199

^aEthanol Reflux

^bIrradiation was performed at 120°C, 65 W, 2bar with High absorption level.

^c yield obtained with the column chromatography purification.

The structure of these ethyl 7,7-dimethyl-5-oxo-4-aryl-2-[(arylsulfonyl)methyl]-1,4,5,6,7,8-hexahydroquinoline-3-carboxylates in accord with elemental analyses and ^1H , ^{13}C and 2D NMR spectroscopic data as illustrated for a representative example **37b**. In the ^1H NMR spectrum of **13b**, hydrogens at C-1 appeared as a two doublets at 2.14 & 2.22 with the J value of 12 Hz, which showed HMBs with C-6 at 193.3 ppm and C-11 at 28.2 ppm (Figures 3 & 4).

The C-17-CH₂ hydrogens (methylene hydrogens of ester function) appeared as quartet at 4.02 ppm ($J = 6\text{ Hz}$), which showed HMBs with C-9 at 93.2 and C-10 at 35.0 ppm. The methylene hydrogens of the ester function appeared as a quartet at 3.88 ppm which showed HMBC with ester carbonyl at 164.1 ppm and CH₃ carbon at 13.9 ppm. The carbonyl carbon C-6 that appears at 193.3 ppm showed HMBC correlation with C-11 & 12 hydrogens at 0.95 ppm.

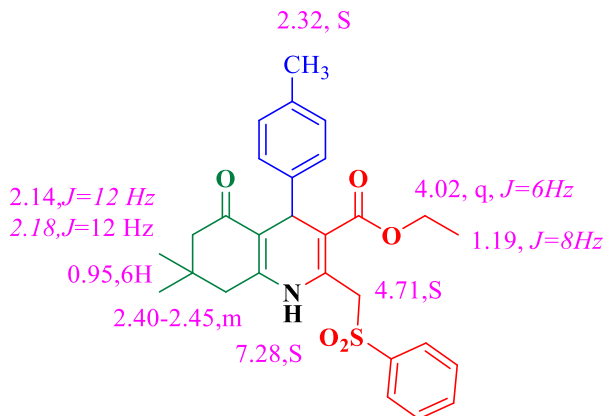


Figure 3. Selected ^1H NMR values for compound **13b**

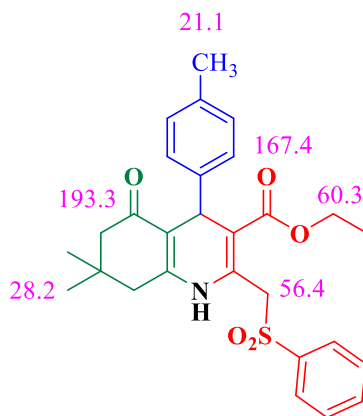


Figure 4. Selected ^{13}C NMR values for compound **13b**

Selective cyclooxygenase (COX-1 & COX-2) inhibitor studies of ethyl 7,7-dimethyl-5-oxo-4-aryl-2-[(arylsulfonyl)methyl]-1,4,5,6,7,8-hexahydroquinoline-3-carboxylates **13**

The test compounds were subjected to *in vitro* cyclooxygenase (COX) inhibition assays. The IC₅₀, the concentration of compounds that provided 50% inhibition of COX-2 and COX-1, was calculated. IC₅₀s of the test compounds **37 a-p** and celecoxib for inhibition of COX-1 were 24.8, 23.8, 18.2, 16.5, 12.8, 13.5, 21.4, 14.3, 17.6, 21.7, 23.5, 19.5, 17.9

14.7, 13.6, 11.5 and 14.2 μM , respectively. IC₅₀ values for COX-2 inhibition were found to be 0.08, 11.2, 1.5, 1.2, 0.9, 12.6, 9.1, 2.1, 3.1, 0.4, 1.6, 0.9, 1.4, 2.1, 2.8, 1.8 and 2.2 μM , respectively. Selectivity indices or the ratio of IC₅₀ for COX-1 inhibition to that of COX-2 of the test compounds and celecoxib were 2.1, 12.3, 13.7, 14.2, 1.07, 2.3, 6.8, 5.6, 54.2, 14.6, 21.6, 21.6, 12.7, 7.0, 4.8, 6.3, 6.4 and 310, respectively. The results are shown in Table 3.

Table 3. selective cyclooxygenase (COX-1 & COX-2) inhibitor studies of ethyl 7,7-dimethyl-5-oxo-4-aryl-2-[(arylsulfonyl)methyl]-1,4,5,6,7,8-hexahydroquinoline-3-carboxylates **13**

Code	Ar	Ar'	IC ₅₀ (M) ^a		COX-2 S.I. ^b
			COX-1	COX-2	
13a	<i>p</i> -ClC ₆ H ₄	<i>p</i> -MeOC ₆ H ₄	23.8	11.2	2.1
13b	<i>p</i> -ClC ₆ H ₄	<i>p</i> -MeC ₆ H ₄	18.2	1.5	12.3
13c	<i>p</i> -ClC ₆ H ₄	<i>p</i> -ClC ₆ H ₄	16.5	1.2	13.7
13d	<i>p</i> -ClC ₆ H ₄	<i>p</i> -FC ₆ H ₄	12.8	0.9	14.2
13e	C ₆ H ₅	<i>p</i> -MeOC ₆ H ₄	13.5	12.6	1.07
13f	C ₆ H ₅	<i>p</i> -MeC ₆ H ₄	21.4	9.1	2.3
13g	C ₆ H ₅	<i>p</i> -ClC ₆ H ₄	14.3	2.1	6.8
13h	C ₆ H ₅	<i>p</i> -FC ₆ H ₄	17.6	3.1	5.6
13i	<i>p</i> -Me-C ₆ H ₄	<i>p</i> -MeOC ₆ H ₄	21.7	0.4	54.2
13j	<i>p</i> -Me-C ₆ H ₄	<i>p</i> -MeC ₆ H ₄	23.5	1.6	14.6
13k	<i>p</i> -Me-C ₆ H ₄	<i>p</i> -Cl-C ₆ H ₄	19.5	0.9	21.6
13l	<i>p</i> -Me-C ₆ H ₄	<i>p</i> -F-C ₆ H ₄	17.9	1.4	12.7
13m	<i>p</i> -Me-C ₆ H ₄	<i>o</i> -MeOC ₆ H ₄	14.7	2.1	7.0
13n	C ₆ H ₅	<i>o</i> -MeC ₆ H ₄	13.6	2.8	4.8

13o	C ₆ H ₅	<i>o</i> -Cl-C ₆ H ₄	11.5	1.8	6.3
13p	C ₆ H ₅	<i>o</i> -NO ₂ -C ₆ H ₄	14.2	2.2	6.4
Celecoxib			24.8	0.08	310

^aValues of ovine COX-1/COX-2, are mean values of two determinations acquired

where the deviation from the mean is < 10%.

^b (COX-1 IC50/ COX-2 IC50). *In-vitro* COX-2 selectivity index

CONCLUSION

In this article we described a four-component domino reaction of ethyl-3-oxo-4-(arylsulfonyl)butanoates, aromatic aldehydes, dimedone and ammonium acetate under microwave irradiation under solvent free condition to synthesize ethyl 7,7-dimethyl-5-oxo-4-aryl-2-[(arylsulfonyl)methyl]-1,4,5,6,7,8-hexahydroquinoline-3-carboxylates 83. This method provides many superiority like simplicity, very high yield and environment friendly. The reaction proceed through the Hantzsch condensation reaction. The synthesized compounds were subjected to selective cyclooxygenase-2 (COX-2) inhibitor evaluation studies and shows considerable activity.

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