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A B S T R A C T

A series of novel 4-[(arysulfonyl)methyl]-2H-chromen-2-ones by the reaction of phenol derivatives with ethyl 3-oxo-4-(arylsulfonyl) butanone using a green catalyst Montomorillonite K-10 clay at 80°C under solvent free condition. The prepared compounds were screened for anti-fungal activity studies Many of the compounds shown remarkable anti-fungal activity against the tested organisms.

***Key words*:** 4-[(arysulfonyl)methyl]-2H-chromen-2-ones, Montomorillonite K-10 clay, Anti-fungal activity

Numerous number of compounds, having chromen-2-one moiety (2H-benzopyran-2-one) are notable heterocycles, used in the world of synthetic organic chemistry and natural products [1-2]. Commercially few alkaloids having chromen-2-one nucleus such as ningalin B_1 and lamellarin D_2 are well known to display cytotoxicity, immune-modulatory activity and HIV-1 integrase inhibition [3-5]. Many chromen-2-one derivatives showing biological activity are summarized in (Fig 1). 4-Hydroxy-3-(3-oxo-1-phenylbutyl)-2H-chromen-2-one known as Warfarin 10 (Fig 2) was a well-known compound used to reduce secondary malignant growth of intestinal cancers to a significant extend [6] and also effectively used as an adjunct to the surgical procedure of malignant carcinomas [7]. Besides, 7,8-dihydroxy-2H-chromen-2-one, namely daphnetin 11 (Fig 2) was efficiently used to prevent epidermal growth factor receptor [EGFR], Protein kinase C, Serine-threonine specific protein kinase and tyrosine kinase in vitro [8]. The focus in developing new methods for the synthesis of highly functionalized pyrido coumarins (5H-Chromeno[4,3-b]pyridine-5-one derivatives have been organized by the variable range of their biological activity [9]. For (e.g.), anti-cancer activities have been exhibited by compounds 13 a, b – 15a, [10] many number of alkaloids. Compound 15b well known for anti-inflammatory activity, [11] compound 16, has specific anti-bacterial activity [12]. Few other inhibitors were well known, like compound 13a, known to inhibit topoisomerases I, for as much as compound 13b, for topoisomerases II and aromatic activity was shown by compound 14, Besides, the mentioned structural nucleus is present in many number of alkaloids. Natural chromeno pyridines is known presently which covered compounds 17a-c, Phochrodines A-C, which were isolated from mangrove endophytic fungus *Phomopsis sp*., [13] ganocalicines A and B, Compounds 18 a, b exhibited antiallergic activity isolated from *Ganoderma calidophilum*, ganocochlearine G, compound 18c isolated from Ganoderma cochlear [14] and cochlear A, [15] compound 19 (Fig 3) which act as an inhibitor of T-type calcium channels.

The antifungal activity of the synthesized 4-[(arylsulfonyl)methyl]-2-chromene derivatives was evaluated *in vitro* against a panel of pathogenic fungi including *Aspergillus niger*, *Candida albicans*, and *Fusarium oxysporum*, which are known to cause significant infections in humans, animals, and plants. The efficacy of these compounds was determined using standard microbiological techniques such as the measurement of zones of inhibition, minimum inhibitory concentration (MIC), and percentage growth inhibition. The results revealed that structural variations, particularly the electronic and steric properties of aryl substituents on the sulfonyl group, played a crucial role in modulating antifungal potency. Certain derivatives demonstrated marked antifungal activity, in some cases comparable to or exceeding that of widely used commercial antifungal agents like fluconazole and ketoconazole, indicating their potential as promising candidates for further pharmaceutical development.

The study titled *"A Green Approach to the Synthesis of 4-[(Arylsulfonyl)Methyl]-2-Chromenes using Montmorillonite K-10 as a Catalyst and Evaluation of their Antifungal Activity"* presents an environmentally friendly method for synthesizing biologically active chromene derivatives. Utilizing Montmorillonite K-10, a naturally occurring and reusable clay catalyst, the reaction proceeds under mild and solvent-free or eco-friendly conditions, adhering to green chemistry principles.

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The multicomponent reaction involves 2-hydroxybenzaldehyde, malononitrile, and arylsulfonylmethyl compounds to yield 2-chromenes efficiently, with excellent yields and minimal waste. The synthesized compounds were structurally confirmed using FTIR, NMR, and mass spectrometry and evaluated for their antifungal properties against various fungal strains. Some derivatives exhibited significant antifungal activity, especially those with electron-withdrawing groups on the aryl ring, indicating potential for pharmaceutical or agrochemical applications. This work highlights the dual benefit of sustainable synthetic methodology and the discovery of biologically potent molecules.

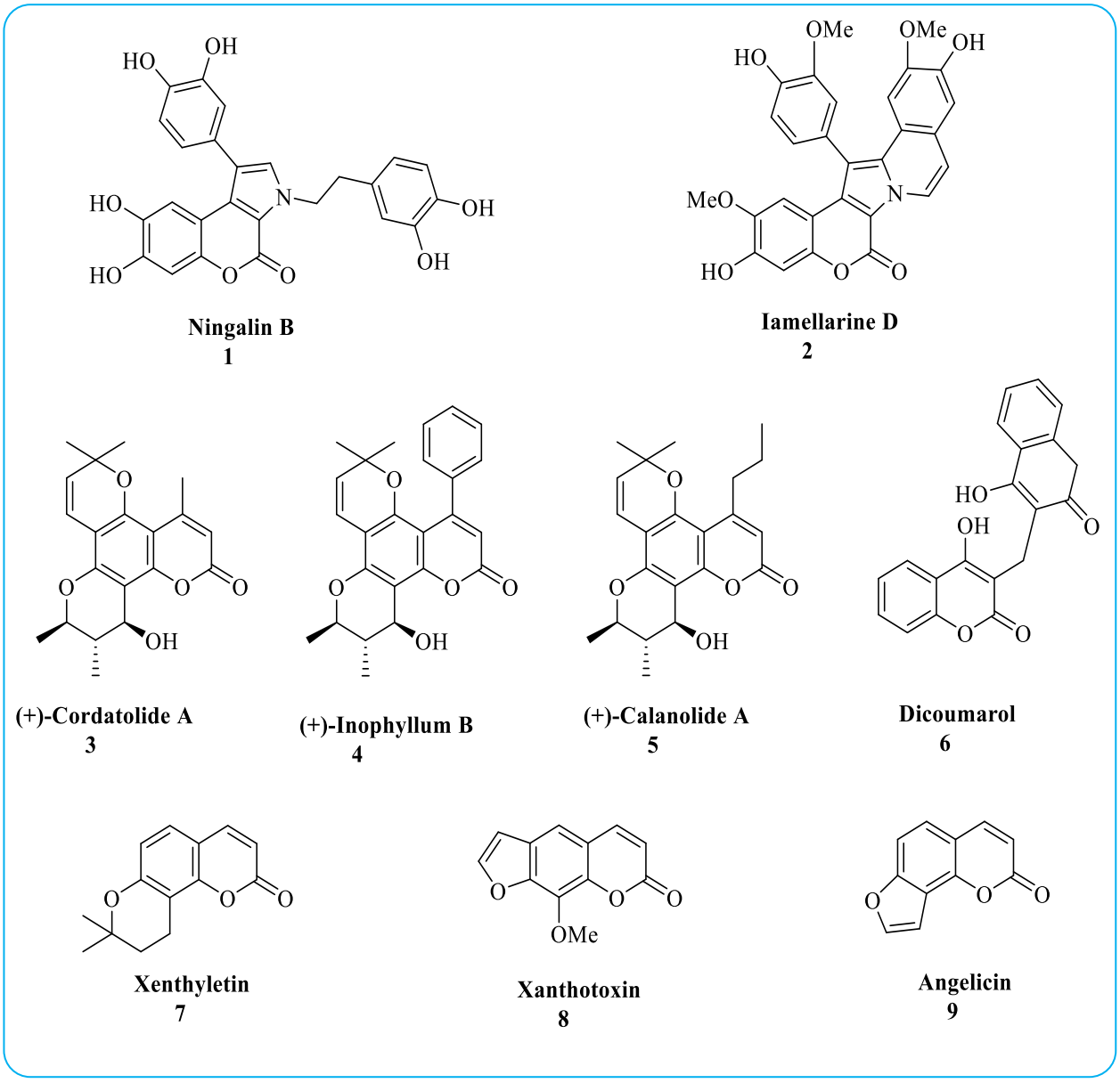


Fig 1 Biologically active and commercially important Chromen-2-one derivatives

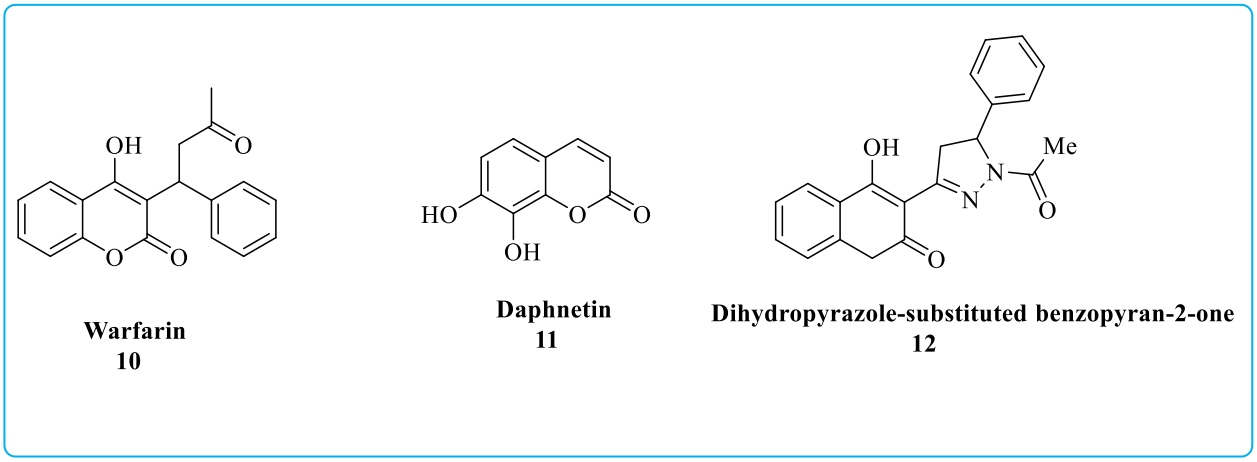


Fig 2 Anticancer and Kinase inhibitors

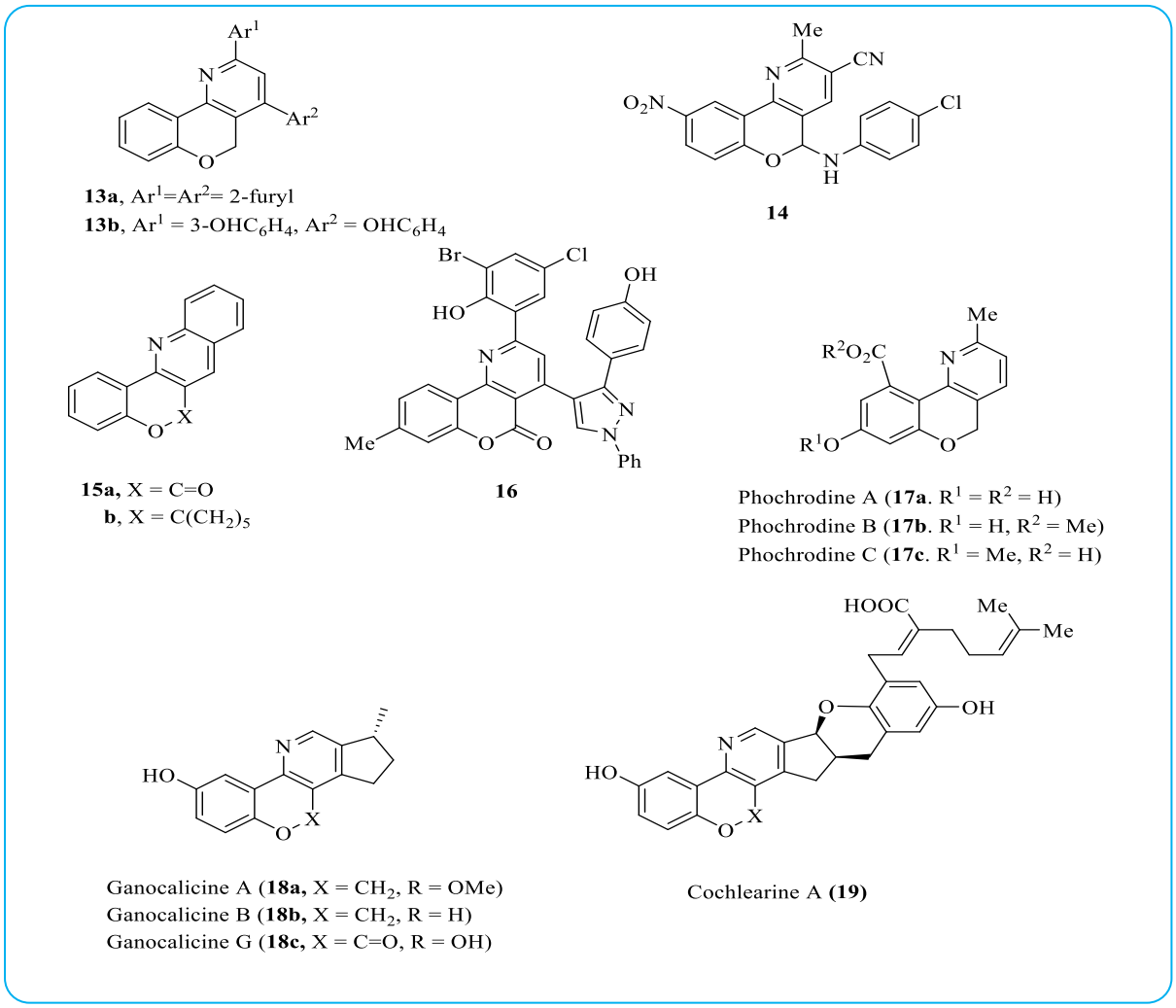
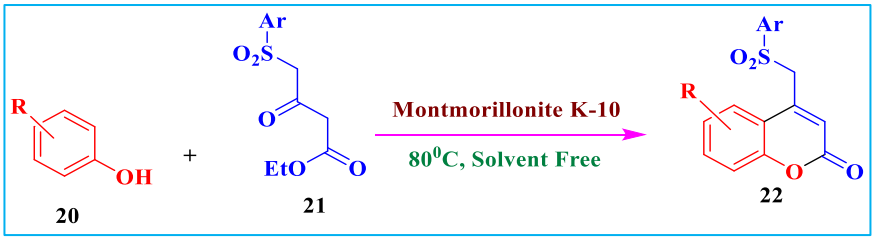


Fig 3 synthetic and natural chromeno[4,3-b]pyridine derivatives

RESULTS AND DISCUSSION

In the present investigation a series of novel 4-[(arysulfonyl)methyl]-2H-chromen-2-ones 22 by the reaction of phenol derivatives 20 with ethyl 3-oxo-4-(arylsulfonyl)butanone 21 using a green catalyst montmorillonite K-10 clay at 80ºC under solvent free condition (Scheme 1). The prepared compounds were screened for anti-fungal activity studies Many of the compounds shown remarkable anti-fungal activity against the tested organisms.



Scheme 1 Synthesis of 4-[(arysulfonyl)methyl]-2H-chromen-2-ones 51

The usage of heterogenous catalysis become an eminent field for the synthesis of organic compounds [16]. Now-a-days the utilization of renewable sources as a synthons in the preparation of pharmaceutical products becoming very popular [17]. The interesting and useful clay catalyst was to be MK-10 [18]. It was found that MK-10 act as a Lewis acid and act as a safe catalyst [19]. In the synthesis of 4-[(arysulfonyl)methyl]-2H-chromen-2-one derivative 22, we first iniate with the optimation of reaction condition regarding reaction time, solvent and catalyst (Table 1). Ethanol as a solvent and solvent free condition were used. The catalyst utilized were $ZrOCl_2.8H_2O$, Oxalic acid, Conc.H_2SO_4, $AlCl_3$, Montmorillonite K-10, $SnCl_2$, $CeCl_3$. The temperature maintained are given the (Table 1). Product 22 obtained in maximum yield when montmorillonite K-10 used as a catalyst under solvent free condition at 80°C.

Thereafter a mixture of phenol derivatives 20 and ethyl-3-oxo-(arylsulfonyl)butanoates 21 along with Montmorillonite K-10 (10 mol%) was stirred for the time 6-8 min at 80ºC. After the completion of the reaction, ethanol was added and the reaction mixture was filtered. The filtrated was poured into the ice water to the crude product. This was filtered and dried. Pure compound 22 was obtained by the purification using column chromatography using petroleum ether/ ethylacetate (4:1) mixture as an eluent. Yield and the melting point of 22 are given in the (Table 2).

Table 1 Catalyst and solvent optimation for the synthesis of 22

Entry	Catalyst	Solvent	Temperature	Time	Yield (%)
1	$ZrOCl_2.8H_2O$	Ethanol	Reflux condition	2 hrs	80
2	Oxalic acid	Ethanol	Reflux condition	2 hrs	82
3	Conc.H_2SO_4	Nil	RT	3 hrs	75
4	$AlCl_3$	Ethanol	Reflux condition	3 hrs	78
5	Montmorillonite K-10	Nil	80 °C	8 min	95
6	$SnCl_2$	Ethanol	Reflux condition	2 hrs	85
7	$CeCl_3$	Ethanol	Reflux condition	2 hrs	88

Table 2 Synthesis of compound 22
Yield, reaction time and melting point of compound 22

Code	R	Ar	Reaction time (min)	Yield (%)	Melting point (°C)
22a	2-NO_2	C_6H_5	8	92	210-211
22b	H	C_6H_5	7	90	217-218
22c	4-Cl	*p*-ClC_6H_4	7	88	219-220
22d	2- NO_2	*p*-ClC_6H_4	6	96	204-205
22e	4-Cl	*p*-ClC_6H_4	6	94	21-215
22f	4-Br	C_6H_5	6	92	220-221
22g	4-Me	C_6H_5	6	90	208-209
22h	4-OMe	C_6H_5	6	94	201-202
22i	3-OH	C_6H_5	6	95	212-213

The structure of these 4-[(arysulfonyl)methyl]-2H-chromen-2-ones in accord with elemental analyses and ^1H, ^{13}C and 2D NMR spectroscopic data as illustrated for a representative example 51i. In the proton NMR spectrum of 51i, a singlet appears at 4.63 ppm is due to the methylene protons. Also, it exhibits HMBC correlation C-14, C-10 and C-9 whose carbon peaks appears at 139.4, 159.3 and 104.4 ppm respectively. The C-1 carbon proton appears as a doublet with the *J* value of 12 Hz nd also shows HMBC correlation with C-10 and C-3 carbon, those appears at 111.0 &104.3 ppm in carbon spectrum. The carbonyl carbon peak lies on 162.3 ppm and the –OH proton appears at 9.98 ppm.

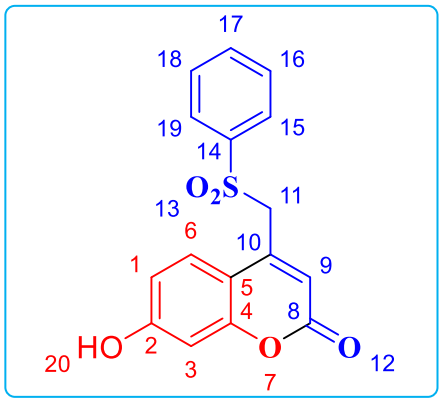


Fig 4 Atomic labeling of compound 22i

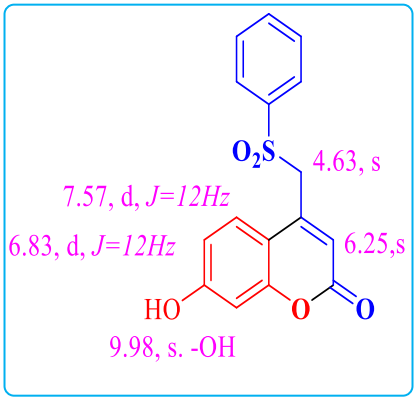


Fig 5 Selected ^1H NMR values for compound 22i

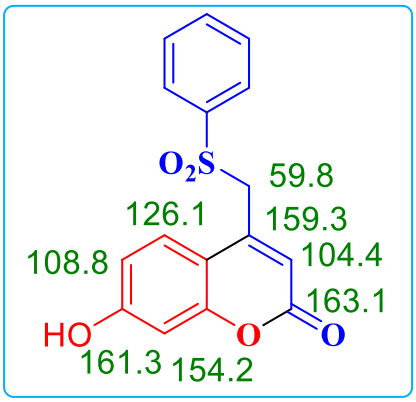


Fig 6 Selected ^{13}C NMR values for compound 22i

Anti-fungal studies

Compounds synthesized were investigated for antifungal studies. Most of the compounds show considerable activity against all the organisms tested. Compounds 22a, 22b, 22e and 22h were found to be almost equipotent to that of reference drug kanamycin (Table 3).

Table 3 Antifungal activity 4-[(arysulfonyl)methyl]-2H-chromen-2-ones 22

S. No.	Comp	*Aspergillus Niger* Concn. (mmol)				*Trichoderma* Concn. (mmol)				*Candida albicans* Concn. (mmol)			
		25	50	75	100	25	50	75	100	25	50	75	100
1	22a	++	++	+++	++++	+	+	++	++	++	++	+++	+++
2	22b	-	-	++	++	+	++	+++	+++	-	+	+	++
3	22c	+	+	++	++	-	-	-	-	-	-	-	-
4	22d	++	++	++	+++	-	-	-	++	+	+	++	++
5	22e	++	+++	+++	++++	+	+	++	++	-	-	+	++
6	22f	-	-	-	-	+	++	++	+++	-	-	-	-
7	22g	+	++	++	+++	-	-	-	-	-	-	-	-
8	22h	-	-	-	++	+	++	+++	+++	+	+	++	+++
9	22i	-	+	+	++	-	-	+	+	-	-	-	-
10	*Kanamycin*	++	++	+++	+++	++	+++	+++	++++	+	++	+++	+++

CONCLUSION

In this article describes synthesis of a series of novel 4-[(arysulfonyl)methyl]-2H-chromen-2-ones by the reaction of phenol derivatives with ethyl 3-oxo-4-(arylsulfonyl)butanone using a green catalyst Montmorillonite K-10 clay at 80 °C under solvent free condition. The prepared compounds were screened for anti-fungal activity studies Many of the compounds shown remarkable anti-fungal activity against the tested organisms.

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