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Reaction of Malonamide with schiff bases of benzal-4-Fluoroaniline and evaluation of products for their antifungal activity

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Abstract
Condensation of malonamide with benzal-4-fluoroaniline and its C-phenyl derivatives (I-VIII) resulted in the formation of solid compounds. The products have been identified as addition- elimination products viz. benzalmalonamide and its derivatives (la-VIIIa) respectively on the basis of elemental analysis, spectral studies and m.m.p. determination (no depression) with an authentic sample. The results are at a variance as compared to similar condensation of malonamide with benzalaniline. The compounds la-VIIIa were tested *in vitro* for their antifungal activity against *Alternaria alternata*, *Fusarium oxysporum*, *Myrothecium roridum*, *Helminthosporium gramineum* and *Colletotrichum capsici* by spore germination inhibition method. 3,4-Dimethoxybenzalmalonamide (Va) has been found to be most effective compound of the present study.

Keywords: Condensation, malonamide, benzal -4- fluoro aniline, antifungal activity

Introduction
Condensation of active methylene compounds with benzalanilines [1] has been reported to yield either addition products or addition-elimination products depending on the active methylene compound, nature of substituents present and the reaction conditions. Active methylene compounds with at least one cyano group have been thoroughly investigated for their chemical behaviour towards benzalaniline and substituted benzalanilines [2-6]. The biological potential of the products has also been studied [7-10] The aim of the present work is to study the effect of presence of fluoro substituent in the N-phenyl nucleus of benzalanilines on their reaction with malonamide and to evaluate the products for their antifungal activity and the results of this study are being communicated in this manuscript.

Materials and methods
Reaction of Malonamide with benzal-4-fluoroaniline Benzal-4-fluoroaniline / substituted benzal-4- fluoroaniline (0.01 mole) was dissolved in benzene (20 ml) in a conical flask. To this solution was added malonamide (0.01 mole) and a few drops of pyridine. The reaction mixture was warmed and stirred and allowed to stand at room temperature overnight. The solid which separated out was filtered and recrystallized from ethanol to get the crystals of the respective product.

***In vitro* screening for antifungal activity:** The stock solution of each compound was prepared by dissolving each chemical (20 mg) in absolute alcohol (0.5 ml) and volume was made to 10 ml with sterilized distilled water. The stock solution of 2000 ppm of each compound thus prepared on active ingredient basis was kept in refrigerator till use. The required dilutions of 1000, 500, 250, 100 and 50 ppm were subsequently made from the stock solution by adding sterlized distilled water as and when required.

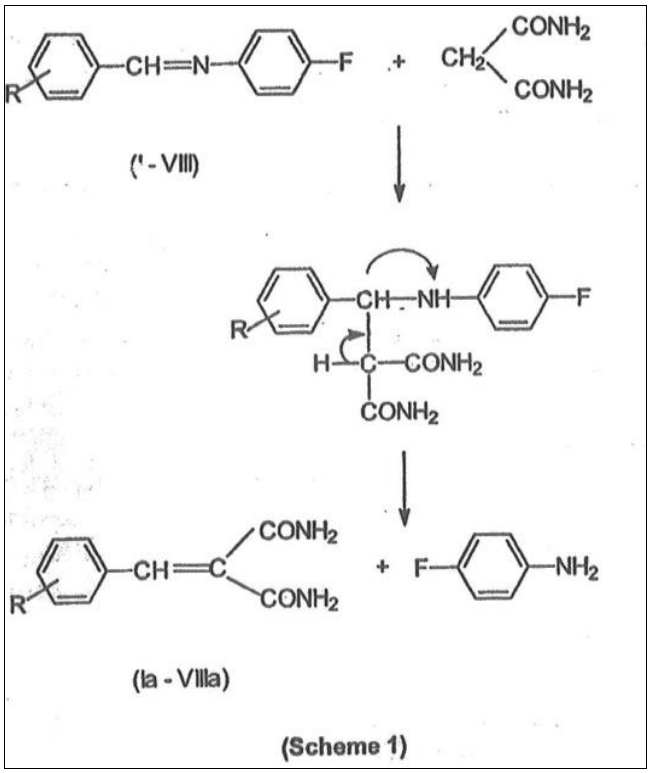
Small droplets (0.02 ml) of spore suspension in equal quantity with solution of the test compound were seeded in the cavities of the slides. These slides were placed in petri plates lined with moist filter paper and incubated at 25 ± 1°C for 20 hours. The germination of spores was recorded and percent spore germination inhibition was - calculated by using the formula:

$$\text{Percent spore germination inhibition} = \frac{\text{Spore germination in control} - \text{Spore germination in treatment}}{\text{Spore germination in control}} \times 100$$

The antifungal activity has been expressed in terms of EDso values (effective dose to inhibit 50 per cent spore germination) calculated by plotting the percent spore germination inhibition values against different concentrations of the compounds on the graph paper.

Results and discussion
Condensation of malonamide with benzal-4- fluoroaniline and its C-phenyl derivatives (I-VIII) in equimolar ratio has resulted in the formation of solid products Ia-VIIIa respectively. The products have been identified as addition-elimination products viz. benzalmalonamide (Ia), 4-chlorobenzalmalonamide (IIa), hydroxybenzalmalonamide (IIIa), methoxybenzalmalonamide (IVa), 4- 4- 3,4-dimethoxybenzalmalonamide (Va), 3,4,5-trimethoxybenzalmalonamide (VIa), 3-methoxy-4-hydroxybenzalmalonamide (VIIa) and 3-ethoxy-4-hydroxybenzalmalonamide (VIIIa) respectively on the basis of elemental analysis, spectral studies and m.m.p. determination (no depression) with an authentic sample prepared by condensing malonamide with respective aldehyde. The IR spectra of these compounds contain bands at 1628 to 1664 cm¹ which are assigned to carbonyl group and a broad band at 3390 cm³¹ which is indicative of the amide linkage. The PMR spectra of the compounds in CDCl, show two close bands at 6.9 8 and 7.1 8 for two protons each indicating the presence of amide protons in addition to the characteristic bands of groups present in the respective molecule. For instance the PMR spectrum of 4-chlorobenzalmalonamide (IIa) shows a one proton singlet at

8.2 8 for benzalic ($ClC_6H_4CH=C<$) proton, two bands of two protons each at 7.3 δ and 7.6 δ for four aromatic protons and two close bands at 6,9 δ and 7.1 δ for two protons each for four protons of amide groups, thus, accounting for all the nine protons present in the molecule.



(Scheme 1)

The results of this study on the reaction of malonamide with benzal-4-fluoroanilines are at variance as compared to similar condensation of malonamide with benzalaniline where addition product has been reported[1]. The presence of fluoro substituent in the N-phenyl nucleus of benzalanilines, it seems, facilitates the formation of addition-elimination product rather than addition product. The carbanion formed from malonamide adds to the carbon-nitrogen double bond of the benzal-4-fluoroaniline to give unstable addition product which losses the amine molecule to yield the stable addition-elimination product (Scheme 1). The benzalmalonamides along with their characteristics are recorded in Table-1.

Table 1: Characteristics of Benzalmalonamides

Compound	R	m.p. ^{0}C	Yield %	Molecular formula*
Ia	H	80	50	$C_{10}H_{10}N_2O_2$
IIa	4-Cl	122	56	$C_{10}H_9N_2O_2Cl$
IIIa	4-OH	168	68	$C_{10}H_{10}N_2O_3$
IVa	4-CH_3	110	58	$C_{11}H_{12}N_2O_3$
Va	3-OCH_3 4-OCH_3	87	74	$C_{12}H_{14}N_2O_4$
VIa	3-OCH_3 4-OCH_3 5-OCH_3	90	60	$C_{13}H_{16}N_2O_5$
VIIa	3-OCH_3 4-OH	125	65	$C_{11}H_{12}N_2O_4$
VIIIa	3-OC_2H_5 4-OH	172	55	$C_{12}H_{14}N_2O_4$

*All the compounds gave satisfactory elemental analysis

Table 2: Antifungal activity of benzalmalonamides

Compound	ED_{50} values (ppm) aganist				
	A. alternata	*F. oxysporum*	*C. capsict*	*H. gramineum*	*M. roridum*
Ia	*	*	*	*	*
IIa	140	*	*	390	*
IIIa	*	*	670	*	600
IVa	720	*	310	*	760
Va	680	170	380	300	160
VIa	720	*	310	*	760
VIIa	340	630	300	630	950
VIIIa	*	*	350	*	160

*more than 1000 ppm

The compounds Ia-VIIIa were tested *in vitro* for their antifungal activity against *Alternaria alternata*, *Fusarium oxysporum*, *Myrothecium roridum*, *Helminthosporium gramineum* and *Colletotrichum capsici* by spore germination inhibition method [11] at various concentrations. The results are expressed in terms of ED_{50} values in Table-2. Only five compounds have ED_{50} value less than 1000 ppm against A. alternata and the best among them is Ila with ED_{50} value of 140 ppm. 3,4-Dimethoxylbenzalmalonamide (Va) has been found to possess promising activity against Foxysporum and M. roridum with ED_{50} values of 170 and 160 ppm respectively. This compound is also the most effective among the test compounds against H. gramineium with ED_{50} value of 300 ppm. The most effective compound against C. capsici has been 4-hydroxy. -3-methoxybenzalmalonamide (VIIA) with ED_{50} value of 300 ppm. 4-Hydroxy-3-ethoxybenzalmalonamide (VIIIA) possesses promising activity against M. roridum with ED_{50} value of 160 ppm. Thus, the most promising compound of the present study is 3,4-dimethoxybenzalmalonamide (Va). In general, the substitution of phenyl ring increases the antifungal activity of the parent compound (la), more so if the substituent is electron-releasing.

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