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SYNTHESIS OF NOVEL THIAZOLIDINONE BEARING ACRIDIN-9-ONE MOIETY AS ANTIMICROBIAL AGENTS

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ABSTRACT

To synthesize some novel thiazolidinone bearing acridinone moiety by using various aromatic aldehydes. The newly synthesized compounds were screened for microbiological screening. A series of 5-arylidene-3-(2-phenyl-4-oxo-1,3-thiazolidine) acetohydrazido acridin-9-one have been synthesized via condensation of 3-(2-phenyl-4-oxo-1,3-thiazolidine) acetamido acridin-9-one with various aromatic aldehyde. These compounds confirmed by physical (TLC and M.P.) and spectral data (IR, NMR and MASS) and were subjected to microbiological screening viz antibacterial and antifungal activity. All the synthesized compounds proved to have potent antimicrobial activity against Gram positive, Gram negative and Fungal organism.

KEYWORDS: *Thiazolidinone derivatives, Ullmann condensation, acridin-9(10H)-one, antimicrobial activity*.

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INTRODUCTION

Human kind has been subject to infection by microorganisms since before the dawn of recorded history. One presumes that mankind has been searching for suitable therapy for nearly as long. During the past 80 years one of the most important therapeutic advances in the history of medicine is chemotherapy, a word coined by Paul Ehrlich explaining that chemotherapeutic agents are the chemicals that are intended to be toxic for pathogenic organisms but innocuous for the host.[1] The search for 'better medicines for a better world' is a never-ending process to help the suffering mankind from dreadful and fatal ailments. The manifold increase in the momentum of research and discovery of newer molecules has resulted in accelerated growth and spectacular advancement of science and basic research during the past few decades and 'gifted' some really 'wonder drugs' to the therapeutic spectrum of medicines.[2] Heterocyclic compounds containing sulphur and nitrogen atoms represent a very important group of organic compounds, which exhibit significant biological activity and show various pharmacological effects. These classes of compounds are known as 'Thiazolidines' and 'Azetidinones'. This has given a big blow to the bacterial and fungal resistance by many of the drugs and antibiotics.[3] Compounds carrying the thiazolidinone ring have been reported to demonstrate wide range of pharmacological activities, like antibacterial, antifungal, anti-inflammatory, analgesic,[4] antitubercular,[5] anticonvulsant,[6] antihistaminic, anaesthetic, antithyroid, antiparkinsonism, anticancer, antimalarial, etc.[7-8] Acridine and its derivatives constitute an important series of chemotherapeutic drugs and dyestuffs; they are bactericidal and bacteriostatic against both Gram positive and Gram negative organisms. Acridin-9-(10H)-one, a derivative of acridine, is an interesting compound of tricyclic nitrogen containing heterocyclic and was first used in 19th century against malaria.[9] We synthesize some 5-arylidene-3-(2-phenyl-4-oxo-1,3-thiazolidine) acetohydrazido acridin-9-one derivatives (VIIa-VIIf) from acridinone and various aromatic aldehydes. The structure of newly synthesized compounds were confirmed from spectral data and were screened for microbiological screening.[10]

MATERIALS AND METHODS

All the AR and LR grade chemicals and reagents used in the present project, procured from Aldrich, Hi-Media, Merck, Sigma and Ranbaxy. Melting points of the synthesized compounds were determined by open capillary method and were uncorrected. IR spectral analysis was carried out using FTIR-8400S, SHIMADZU, ^{1}HNMR spectral analysis were carried out using instrument amx-400 and the solvent used was deuterated chloroform and dimethyl sulfoxide. The mass spectral data were recorded from LCMS 2010A, SHIMADZU.

METHODOLOGY

Synthesis of N-phenyl anthranilic acid (I): Ullmann condensation[11]

A mixture of o-chlorobenzoic acid (20g, 0.128mol), aniline (11.8ml, 0.128mol) and copper metal (0.5g) were taken in a round bottom flask, to which 100ml isoamyl alcohol was added, in this mixture 20gm dry potassium carbonate was added and the mixture was refluxed about 6 hrs in a light liquid paraffin oil bath at 135-140°C. The isoamyl alcohol was removed by steam distillation and mixture poured into 2 L of hot water and acidified with concentrated hydrochloric acid. The bluish black precipitate formed was filtered, washed with hot water & collected. The crude acid was dissolved in dil sodium hydroxide solution and boiled by using the activated charcoal. The filtrates acidified with concentrated hydrochloric acid, light yellowish precipitate was obtained, which was washed with hot water. The crude acid was recrystalized from aqueous methanol to give a light yellow solid.

Synthesis of acridin-9(10H)-one[11] (II)

N-Phenyl anthranilic acid (18g, 0.084mol) was taken in a 500ml of round bottom flask to which polyphosphoric acid (180g, 0.5327mol) was added, shaken well and refluxed on a water bath at 100°C for 3 hrs. Appearance of yellow colour indicated the completion of reaction. Then, it was poured into 2 L of hot water and made alkaline by 25% ammonia solution. The yellow precipitate formed was filtered, washed with hot water and collected. The crude acridin-9(10H)-one was recrystalized from acetic acid.

Synthesis of Ethyl ethanoate acridin-9-one[7-8] (III)

Equimolar mixture of acridin-9(10H)-one (0.05 mol, 9.75 g) & ethylchloroacetate (0.05 mol, 6.1 ml) was taken in 500 ml round bottom flask. To this mixture dry acetone (70 ml) and ethanol (40 ml) were added. The reaction mixture was refluxed in presence of anhydrous K_2CO_3 for about 10 hours in water bath. Then cooled & poured the mixture into ice-cold water where the Ethyl ethanoate acridin-9-one gets precipitated. Product was filtered and dried in oven at 125 ˚C.

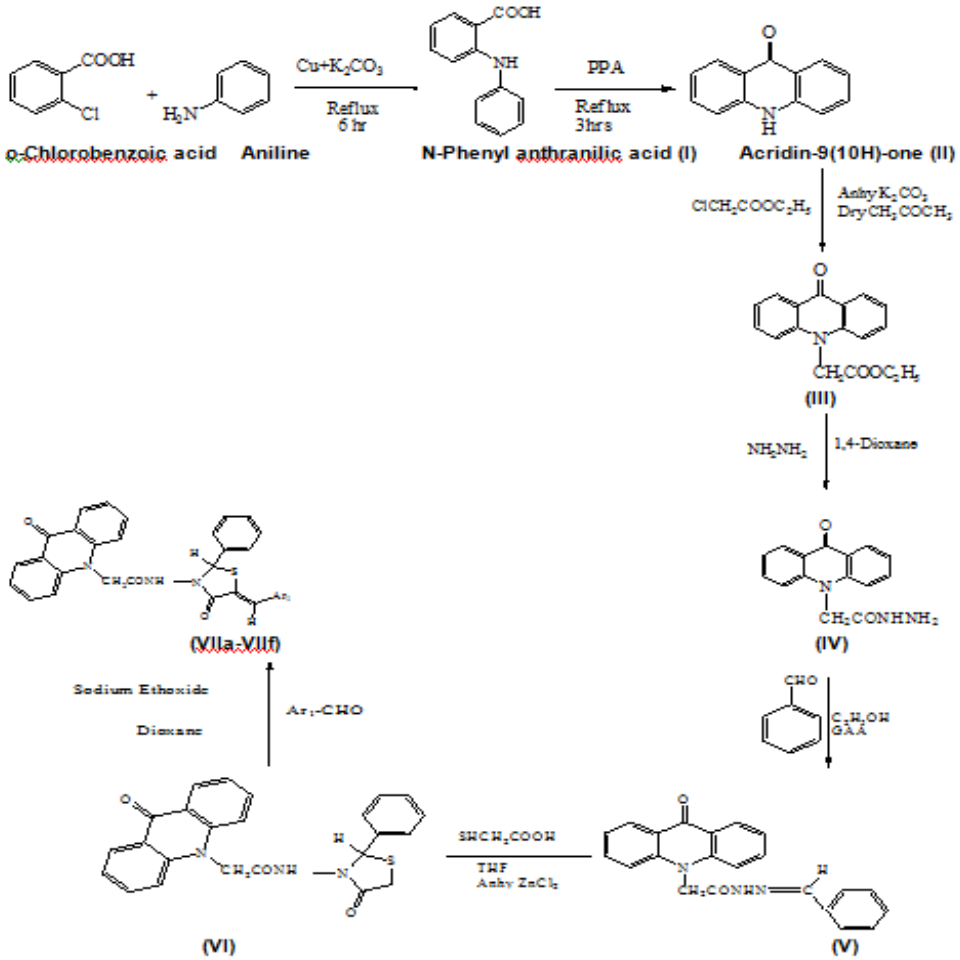
Synthesis of acetohydrazido acridin-9-one[7-8] (IV)

Equimolar mixture of ethyl ethanoate acridin-9-one (0.05 mol, 14.05 g) & hydrazine hydrate (0.05 mol, 1.6 ml) was taken in round bottom flask. To this reaction mixture, 1,4-dioxan (50 ml) was added and reflux about 6 hrs maintaining the temperature 60-70˚C. Soft solid mass had appeared which was filtered, dried and recrystalized with chloroform.

Synthesis of phenyl acetohydrazido acridin-9-one[7-8] (V)

Aetohydrazido acridin-9-one (0.05 mol, 13.35 g) taken in round bottom flask along with 30 ml ethanol. Benzaldehyde (0.05 mol, 5.3ml) was dissolved in 30 ml ethanol and added slowly for about 20 min with vigorous stirring, maintaining the temperature at 40-50˚C. Added four drops of glacial acetic acid and allowed to reflux for further 5 hrs. Poured the mixture into 250 ml ice-cold water and stirred. Precipitate obtained was filtered, dried and recrystalized from chloroform.

Scheme



Compound	Ar_1-CHO
VIIa	benzaldehyde
VIIb	2-nitrobenzaldehyde
VIIc	2-hydroxybenzaldehyde
VIId	3-methoxybenzaldehyde
VIIe	4-chlorobenzaldehyde
VIIf	3,4,5-Trimethoxybenzaldehyde

Synthesis of 3-(2-phenyl 4-oxo-1,3-thiazolidine) acetamido acridin-9-one[7-8] (VI)

Phenyl acetohydrazido acridin-9-one (0.02 mol, 7.1 g) was taken in round bottom flask and mercaptoacetic acid (0.02 mol, 1.84 ml) was added. To this mixture a pinch of anhydrous zinc chloride and THF (60 ml) was added. This mixture was refluxed for about 10 hrs in a heating mantle and allowed to cool, filtered and dried. The product was recrystalized from chloroform.

General method of synthesis of 5-Arylidene-3-(2-phenyl 4-oxo-1,3-thiazolidine) acetohydrazido acridin-9-one[7-8] (VIIa-VIIf)

Equimolar 3-(2-phenyl 4-oxo-1,3-thiazolidine) acetamido acridin-9-one (0.05 mol 21.45gm) & different aromatic aldehydes (0.05 mol) were taken in round bottom flask along with 50 ml dioxane in presence of four drops of sodium ethoxide and allowed to reflux for approximate 7-10 hours. Poured the mixture into 250 ml ice-cold water and stirred. Precipitate obtained was filtered, dried and recrystalized from chloroform.

Antibacterial activity[10]

Antibacterial activity of the synthesized compounds was determined by the cup-plate method against the gram-positive organisms *Staphylococcus aureus, Bacillus subtilis* and gram-negative organisms *Escherichia coli, Pseudomonas aeuroginosa, Shigella* at 50µg/ml concentration. The bacteria were subcultured on Nutrient Agar medium. The petridishes were incubated at 37ºC for 24hr. Ampicillin(10 mcg/disc)(Std.1), Ciprofloxacin(30mcg/disc)(Std.2) and Streptomycin (10mcg/disc)(Std.3) were used as standards. The results are presented in Table2.

Antifungal activity[10]

The antifungal activity of the synthesized compounds was carried out against the fungi *Candida albicans* and *Aspergillus niger* at 50µg/ml concentration. The fungi were subcultured in Sabouraud Dextrose Agar medium. The fungal susceptibility testing was done by cup-plate method using Fluconazole (10 mcg/disc)(Std.1), Amphotericin B (100 units/disc)(Std.2), Clotrimazole (100 mcg/disc)(Std.3) and Griseofulvin (100mcg/disc)(std.4). The petridishes were incubated for 48hr at 25ºC. The results are presented in Table 2.

RESULTS AND DISCUSSION

The newly synthesized compounds were confirmed by various physical and spectral data. These results are given as[7-8,11]:

N-Phenyl anthranilic acid (I)
(m.p. 181°C), IR (KBr), CM^{-1}: 3041 (Ar C-H str.), 1514, 1452 (C=C Ar str), 1658 (C=O str.), 3330 (N-H str.), 2500-3300 (C=O bend. For carboxylic acid)

Acridin-9(10H)-one (II)
(m.p. 340°C), IR (KBr), CM^{-1}: 3352 (N-H str.), 3097, 3062, 3031 (C-H Ar-str.), 1641 (C=O str.), 1535, 1473 (C=C str. aromatic)

Ethyl ethanoate acridin-9-one (III)
(m.p. 210°C), IR (KBr), CM^{-1}: 3078, 3018 (Ar C-H str.), 2943, 2864 (C-H str. alkanes), 1610 (C=O str.), 1591, 1556 (C=C Ar str.), 1292, 1267 (N-CH_2str.); 1H NMR ($CDCl_3$): δ 7.1-8.5(8H, Ar-H), δ 4.6-4.8 (2H, N-CH_2), δ 1.4-1.8 (5H, C_2H_5); MS: (m/z): 281, 282 (M+1), 199, 73

Acetohydrazidoacridin-9-one (IV)
(m.p. 226°C), IR (KBr), CM^{-1}: 3234, 3174 (NH-NH_2str), 3097, 3062, 3031 (C-H Ar str.), 2868 (CH_2-C str.), 1635 (C=O str.), 1565, 1531 (C=C Ar str.), 1379, 1263 (N-CH_2 str.); 1H NMR ($CDCl_3$): δ 7.2-8.4 (8H, Ar-H), δ 3.5-3.9 (3H, NH-NH_2), δ 3.0-3.2 (2H, N-CH_2); MS: (m/z): 267, 268 (M+1), 236, 196

Phenyl acetohydrazido acridin-9-one (V)
(m.p. 272°C), IR (KBr), CM^{-1}: 3481, 3396 (-NH str), 3094, 3064, 3033 (C-H Ar str.), 2956, 2867 (CH_2-C str.), 1633 (CONH str.), 1596, 1571 (C=C str. aromatic), 1290, 1263 (N-CH_2 str.); 1H NMR ($CDCl_3$): δ 8.5 (1H, CONH), δ 7.2-8.4 (13H, Ar-H), δ 2.5-2.7 (1H, N=CH), δ 2.1-2.4 (2H, N-CH_2); MS: (m/z): 355, 356 (M+1), 91

3-(2-Phenyl 4-oxo-1,3-thiazolidine) acetamido acridin-9-one (VI)
(m.p. 217°C), IR (KBr), CM^{-1}: 3475, 3276 (-NH str), 3097, 3033 (C-H Ar str.), 2866 (-N-CH_2-S str.), 1631 (CONH str.), 1596 (C=C Ar str.), 1290, 1265 (N-CH_2 str.), 673 (-CH_2-S-CH); 1H NMR ($CDCl_3$): δ 8.5 (1H, CONH), δ 7.1-8.4 (13H, Ar-H), δ 6.1 (1H, N-CH-Ar), δ 3.6-4.0 (2H, S-CH_2), δ 3.1-3.4 (2H, N-CH_2); MS: (m/z): 429, 430 (M+1), 351, 194, 179, 98

5-Benzylidene-3-(2-phenyl 4-oxo-1,3-thiazolidine) acetohydrazido acridin-9-one (VIIa)
(m.p. 232°C), IR (KBr), CM^{-1}: 3070 (C-H Ar str.), 2873 (-N-CH_2-S str.),v1685 (CONH str.), 1583 (C=C Ar str.), 1325, 1292 (N-CH_2 str.), 659 (-CH_2-S-CH); 1H NMR ($CDCl_3$): δ 8.4 (1H, CONH), δ 6.6-7.8 (18H, Ar-H), δ 4.1 (1H, C=CH-Ar), δ 3.3(1H,S-CH-Ar), δ 2.5-2.9 (2H, N-CH_2); MS: (m/z): 517, 518 (M+1), 352, 336, 265, 236, 194, 91

5-(2-Nitro benzylidene)-3-(2-phenyl 4-oxo-1,3-thiazolidine) acetohydrazido acridin-9-one (VIIb)
(m.p. 265°C), IR (KBr), CM^{-1}: 3103 (C-H Ar str.), 2856 (-N-CH_2-S str.), 1743 (C=O cyclic), 1697 (CONH str.), 1525 (C=C str. aromatic), 1350 (NO_2-C aromatic), 1315, 1271 (N-CH_2 str.), 692 (-CH_2-S-CH)

5-(2-Hydroxy benzylidene)-3-(2-phenyl 4-oxo-1,3-thiazolidine) acetohydrazido acridin-9-one (VIIc)
(m.p. 279°C), IR (KBr), CM^{-1}: 3070, 3001 (C-H Ar str.), 2850 (-N-CH_2-S str.), 1722 (C=O cyclic), 1691 (CONH str.), 1583 (C=C Ar str.), 1325, 1292 (N-CH_2 str.), 667 (-CH_2-S-CH)

5-(3-Methoxy benzylidene)-3-(2-phenyl 4-oxo-1,3-thiazolidine) acetohydrazido acridin-9-one (VIId)
(m.p. 290°C), IR (KBr), CM^{-1}: 3072 (C-H Ar str.), 2852 (-N-CH_2-S str.), 1742 (C=O cyclic), 1683 (CONH str.), 1583 (C=C Ar str.), 1325, 1292 (N-CH_2 str.), 667 (-CH_2-S-CH)

5-(4-Chloro benzylidene)-3-(2-phenyl 4-oxo-1,3-thiazolidine) acetohydrazido acridin-9-one (VIIe)
(m.p. 285°C), IR (KBr), CM^{-1}: 3087 (C-H Ar str.), 2858 (-N-CH_2-S str.), 1710 (C=O cyclic),1691, 1979 (CONH str.), 1596, 1587 (C=C str. aromatic), 1292 (N-CH_2 str.), 702 (C-Cl Str.)

5-(3,4,5-Trimethoxy benzylidene)-3-(2-phenyl 4-oxo-1,3-thiazolidine) acetohydrazido acridin-9-one (VIIf)
(m.p. 281°C), IR (KBr), CM^{-1}: 3091, 3060, 3010 (C-H Ar str.), 2889 (-N-CH_2-S str.), 1683 (C=O cyclic), 1647 (CONH str.), 1558, 1541 (C=C str. aromatic), 1234 (N-CH_2 str.), 628 (-CH_2-S-CH)

Table 1
Physical data of newly synthesized 5-Arylidene-3-(2-phenyl 4-oxo-1,3-thiazolidine) acetohydrazido acridin-9-one derivatives (VIIa-VIIf)

Comp. Code	Ar_1-CHO	Mol. Formula	% Yield	R_f*	M.P.
VIIa	Benzaldehyde	$C_{31}H_{23}O_3N_3S$	64.60%	0.49	232°C
VIIb	2-Nitrobenzaldehyde	$C_{31}H_{22}O_5N_4S$	69.75%	0.56	265°C
VIIc	2-Hydroxybenzaldehyde	$C_{31}H_{23}O_4N_3S$	71.30%	0.51	279°C
VIId	3-Methoxybenzaldehyde	$C_{32}H_{25}O_4N_3S$	54.85%	0.43	290°C
VIIe	4-Chlorobenzaldehyde	$C_{31}H_{22}O_3N_3SCl$	66.00%	0.57	285°C
VIIf	3,4,5-Trimethoxybenzaldehyde	$C_{34}H_{29}O_6N_3S$	68.20%	0.65	281°C

Stationary Phase : Silica Gel G Mobile Phase : Chloroform: Acetone:: 9:1

Table 2
Biological Activity of newly synthesized 5-Arylidene-3-(2-phenyl 4-oxo-1,3-thiazolidine) acetohydrazido acridin-9-one derivatives (VIIa-VIIf)

Comp. Code	Zone of Inhibition (in mm)						
	B.subtilis	**S.aureus**	**E.coli**	**P.aeuroginosa**	**Shigella**	**C.albicans**	**A.niger**
	50 µg	50 µg	50 µg	50 µg	50 µg	50 µg	50 µg
VIIa	14	17	20	17	13	21	13
VIIb	21	23	21	17	15	15	12
VIIc	14	19	20	12	14	12	9
VIId	14	17	15	14	9	17	12
VIIe	16	17	20	22	15	17	11
VIIf	14	14	17	18	12	13	16
Std 1	4	4	NI	8	6	23	19
Std 2	32	38	30	29	39	29	18
Std 3	26	29	20	17	21	17	21
Std 4	--	--	--	--	--	28	19
Control	NI	NI	NI	NI	NI	NI	NI

Note : Average zone diameter in mm of triplicates, NI : No inhibition Control : DMSO

CONCLUSION

All the newly synthesized compounds were subjected to antibacterial and antifungal activity. From the microbiological screening, the data revealed that all the synthesized compounds proved to have antimicrobial activity. The decreasing order of activity of synthesized compounds against Gram positive organism was found to be:

VIIb > VIIe > VIIc > VIIa ≥ VIId > VIIf

The decreasing order of activity of synthesized compounds against Gram negative organism was found to be:

VIIe > VIIb > VIIa > VIIc > VIIf > VIId

The derivatives of 5-(2-nitrobenzylidene)-3-(2-phenyl 4-oxo-1,3-thiazolidine) acetohydrazido acridin-9-one (VIIb) and 5-(4-chlorobenzylidene)-3-(2-phenyl 4-oxo-1,3-thiazolidine) acetohydrazido acridin-9-one (VIIe) show potent antimicrobial activity against Gram positive, Gram negative and Fungal organism compare to other derivatives. Hence, with these encouraging results, the compounds can be further explored for detailed pharmacological and microbiological investigations.

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CONFLICT OF INTEREST

Conflict of interest declared none.

REFERENCES

1. David AW, Thomas LL. Foye's principle of medicinal chemistry. 5th ed. New York: Lippincot Williams and Wilkins; 1974. p. 819-24.
2. Donald JA. Burger's Medicinal Chemistry and Drug Discovery. 6th ed. New Jersey: A John Wiley and Sons; 2007. Vol-2 (Chemotherapeutic agents).
3. Mustafa A, Asker W, Fithy A, Shalabt A, Sobhy M. Action of Grignard reagents. XII. Action of organomagnesium compounds on 5-aralkylidene derivatives of rhodanine and of 3-phenyl-2,4-thiazolidine. J Org Chem 1958;23:1992.
4. Lodhi RS, Srivastava SD, Srivastava SK. Synthesis and biological activity of 2-(substituted aryl)-3-(N^1imidazolyl-acetamidyl)-4-oxo-thiazolidines and their 5-aryldine derivatives. Indian J Chem 1998 Sep;37B: 899-903.
5. Oza H, Joshi D, Parekh H. Synthesis and antitubercular activity of novel thiazolidinone derivatives. Indian J Chem 1998 Aug;37B:822-4.
6. Archana, Srivastava VK, Kumar A. Synthesis of newer indolyl thiadiazoles and their thiazolidinones and formazans as potential anticonvulsant agents. Indian J Pharm Sci 2003;65(4):358-62.
7. Lather V, Chowdary PVR. Synthesis and antimicrobial activity of N'(arylidine hydrazido methyl)-indoles, 2-(substituted aryl)-3-(N'-Indolyl acetamidyl)-4-oxo-thiazolidinones and 5-benzylidene derivatives of thiazolidinones. Indian J Pharm Sci 2003;65(6):576-79.
8. Srivastava SK, Srivastava S, Srivastava SD. Synthesis of 5-arylidene-2-aryl-3- (1,2,4-triazoloacetamidyl)-1,3-thiadiazol-4-ones as antibacterial, antifungal, analgesic and diuretic agents. Indian J Chem 2002 Sep;41B:1937-45.
9. Bansal RK. Heterocyclic chemistry. 3rd ed. New Delhi: New Age International (P) Ltd; 1999. p. 360-65..
10. Richard FDA, Lisa H. Evaluation of a rapid inoculum preparation method for agar disk diffusion susceptibility testing. J Clin Micro 1982;15(2):282-5.
11. Krishnegowda G, Thimmaiah P, Hegde R, Dass C, Peter JH, Thimmaiah KN. Synthesis and chemical characterization of 2-methoxy-N^{10}-substituted acridones needed to reverse vinblastin resistance in multidrug resistant (MDR) cancer cells. Bioorg Med Chem 2002;10:2367-80.

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