International Journal of Drug Development & Research | July-September 2012 | Vol. 4 | Issue 3 | ISSN 0975-9344 | Available online http://www.ijddr.in
Covered in Official Product of Elsevier, The Netherlands
SJR Impact Value 0.03 & H index 2

FULL Length Research Paper
Covered in Index Copernicus with IC Value 4.68 for 2010

Synthesis and Antimicrobial activity of some Quinazolinones Derivatives

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Abstract

Quinazolines are building blocks for approximately 150 naturally occurring alkaloids with a wide variety of biological responses. The substituents present on C-2 and N-3 of the quinazoline molecule plays in critical role in promoting several biological activities.

Hence a new azaisatins derivative containing 4(3H) quinazolinones has been designed and synthesized. Their structures have been elucidated on the basis of elemental analysis and spectral studies. All the compounds synthesized were screened for their potential antimicrobial activities, which exhibited some authentic results towards testing organism invitro and invivo studies.

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Key words:
Quinazoline, azaisatins, antimicrobial.

How to Cite this Paper:
Karumanchi Anupama Devi [1]*, M. Sarangapani [2], Sriram[3] "Synthesis and Antimicrobial activity of some Quinazolinones Derivatives" Int. J. Drug Dev. & Res., July-September 2012, 4(3): 324-327

Article History:----------
Date of Submission: 27-07-2012
Date of Acceptance: 11-08-2012
Conflict of Interest: NIL
Source of Support: NONE

INTRODUCTION

The advancement and changes in the culture and lifestyle the new disease are being existed among the human population which indicated that the search for better drug is still necessary. Fused pyrimidine ring system is well known to possess important biological properties. Quinazoline and potent antibiotics that are known to inhibit the growth of gram positive bacteria and active transplantable tumors [1]. In many derivatives of quinazoline system more common is 4(3H) quinazolinone. First synthetic derivative of quinazoline was 2-cyano-4(3H) quinazolinone. The most common method for the synthetic of 4(3H) quinazolinone is by the condensation of anthranilic acid with amides or primary amines. Quinazolinone derivatives have been reported for potential biological activities like anti-hypertension [2], [3], antifungal, anti-bacterial

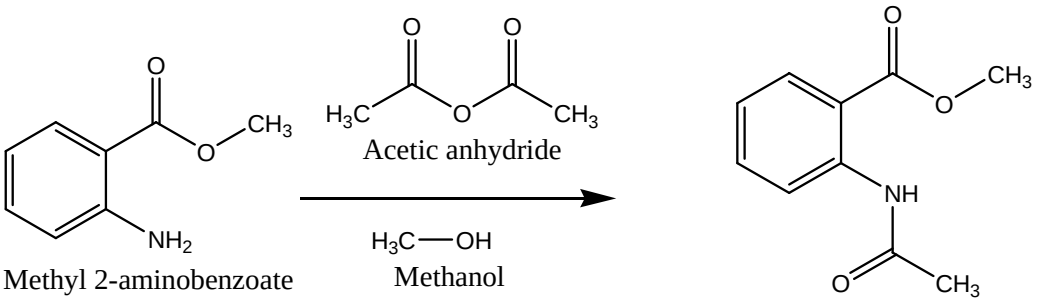
activity [4], [5] anti-cancer [6], anti HIV [7] and pharmacological compounds [8]

Literature survey reveals that azaisatins are biological active compounds that are reported for their application in antibacterial, antifungal, and antiobesity. In view of their biological importance we report the synthesis of new azaisatins derivatives containing 4(3H) quinazolinones. Representative compounds have been characterized for antimicrobial activities.

MATERIAL AND METHODS

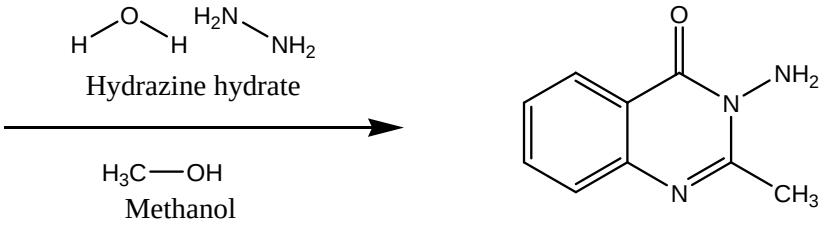
Melting points were recorded by open capillary method and are uncorrected. Purity of compound was confirmed by TLC on silica gel-G using toluene: ethyl acetate (7:3) and iodine vapor as visualizing agent. The IR spectra were recorded on a Perkin Elmer BX 1 spectrometer using KBr cm^{-1}.and ^{1}HNMR on BRUCKER NMR spectrometer (400MHz) using $CDCl_3$ as internal standard. Mass spectra were recorded on an Agilent Mass spectroscopy 1100 series using ESI technique

SCHEME 1

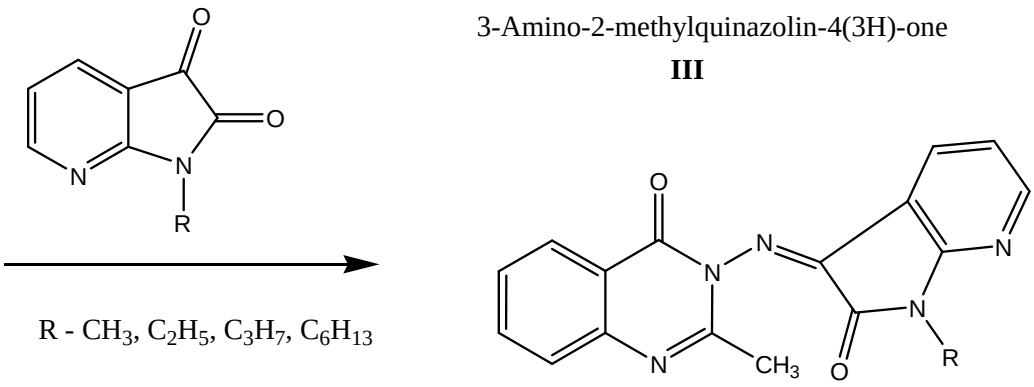


Methyl 2-aminobenzoate
I

Methyl 2-acetamidobenzoate
II



3-Amino-2-methylquinazolin-4(3H)-one
III



R - CH_3, C_2H_5, C_3H_7, C_6H_{13}

IV(a-d)

3-(1,2-Dihydro-1-substituted-2-oxopyrrolo[2,3-*b*] pyridin-3-ylideneamino)-2-methylquinazolin-4(3*H*)-ones

GENERAL PROCEDURE

A) Synthesis of Methyl-2-acetamidobenzoate [9] (II)

In 100ml of round bottomed flask, a solution of Methyl-2-aminobenzoate (I)(0.016 mole) in acetic anhydride (0.0127 mole) were taken and refluxed for 8-12 hours and the reaction was monitored by TLC for completion. The solution was cooled, poured into cold water (50ml) containing a drop of pyridine and stirred until the oil was solidified. The product was filtered, washed with cold water (4x50) and dried. The solid product was recrystallized from ethanol (6ml/gm).

Yield: 80%, m.p: 98 – 100 ^{o} C

B) Synthesis of 3-Amino-2-methylquinazolin-4(3H)-one [9] (III)

In 100ml of round bottomed flask, a solution of hydrazine hydrate (10ml) and Methyl-2-acetoamidobenzoate (II, 0.01 moles) in ethanol were taken and refluxed for 8-12 hours and the reaction was monitored by TLC for completion. The solution was cooled, poured into cold water and the product was filtered, washed with cold water and dried. The solid product was recrystallized from ethanol.

Yield: 84%, m.p: 151 – 152 ^{o} C

C) Synthesis of 3-(1, 2-Dihydro-1-substituted-2-oxopyrrolo [2, 3-b] pyridine-3-ylideneamino)-2-methylquinazolin-4(3H)-ones [10] (IV) a-d

A mixture of 3-Amino-2-methylquinazolin-4(3H)-one (III, 0.001 mole) and substituted azaisatin (0.01 mole) in 10ml of glacial acetic acid were refluxed for 10-15minutes at 140 watt in Catalyst Systems Scientific microwave System and the reaction was monitored by TLC for completion. The resultant solution was poured into cold water. The product was filtered, washed with cold water and dried. The solid product was recrystallized from absolute alcohol.

Table 1: Physical constants of different AZAISATINS Derivatives containing 4-[3H]-quinazolinone.

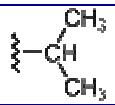
Compound	R	Molecular weight (amu)	Molecular formula	Melting Point	Yield %	Recrystallization solvent
IVa	$-CH_3$	319	$C_{17}H_{13}N_5O_2$	207°C-209°C	75	Absolute Ethanol
IVb	$-C_2H_5$	333	$C_{18}H_{15}N_5O_2$	200°C-202°C	78	Absolute Ethanol
IVc		347	$C_{19}H_{17}N_5O_2$	192°C-194°C	70	Absolute Ethanol
IVd	$-C_6H_{13}$	389	$C_{22}H_{23}N_5O_2$	197°C-198°C	79	Absolute Ethanol

Table 2: Spectral Data

COMPOUND	IR (KBr) cm-1	^{1}H NMR (400 MHz, $CDCl_3$)	MASS SPECTRUM m/z
Synthesis of 3-Amino-2-methylquinazolin-4(3H)-one (III)	3537.96,3302.76 (d,N-H, stretch), 3198.21 (C-H, stretch), 1718.19 (C = O, stretch	δ [ppm]: 8.223 (d, 1H, Ar-H), 7.734 (t,1H,Ar-H), 7.652 (d, 1H,Ar-H), 7.448 (t,1H,Ar-H), 4.907 (s, 2H,NH2), 2.713 (s, 3H, CH3)	The molecular ion was observed at 176.3 $[M+H]^+$
3-(1,2-Dihydro-1-ethyl-2-oxopyrrolo[2,3-b]pyridin-3-ylideneamino)-2-methylquinazolin-4(3H)-one[IV b]	1718.25 (C = O, stretch), 1700.21 (C=O, stretch), 1654.23 (C=N, stretch	δ [ppm]: 8.334 (d, 1H, Ar-H), 8.095 (d, 1H,Ar-H), 6.948 (t, 1H,Ar-H), 7.855 (d,1H,Ar-H), 7.752 (t, 1H,Ar-H), 7.554 (m,2H,Ar-H), 2.320 (s, 3H, CH3) ,3.914 (q, 2H, CH2), 1.33 (t, 3H,CH3)	The molecular ion was observed at 333 $[M^+]$ 372 $[M+K]^+$ and 689 $[2M + Na]^+$

ANTI-MICROBIAL ACTIVITY

Newly synthesized compounds were screened for antibacterial activity against gram positive bacteria *Bacillus subtilis, Staphylococcus aureus, Streptococcus pneumonia* and gram negative bacteria *Escherichia coli, Proteus vulgaris, Klebsiella pneumoniae*, *Pseudomonas aeruginosa* and four fungus *Aspergillus niger, Aspergillus flavus, Candida albicans and Fusarium oxysporium* by using disc diffusion method at 10 µg/disc. The cultural media used for bacteria was nutrient agar medium and for fungi it was potato-dextrose-agar medium. Solutions of Ciprofloxacin and Fluconazole were used as standard antibacterial and antifungal drugs respectively. Amongst all of them compound IVd has been found to be relatively active against gram positive & gram negative bacteria and all four funguses in comparison to other compounds. IVc were moderately active against *Bacillus subtilis, Proteus vulgaris* and all four funguses.

Table 3: Results of Antibacterial Activity

Compounds	µg/ml	*B.subtilis*	*S.aureus*	*S. pneumonia*	*E.coli*	*P.vulgaris*	*K.pneumonia*	*P. aeruginosa*
IV a	10	12	17	10	11	13	11	10
IV b	10	14	13	12	16	16	**19**	12
IV c	10	**18**	12	14	13	**18**	14	12
IV d	10	**20**	**19**	**17**	**20**	**18**	**21**	15
Ciprofloxacin	10	**29**	**28**	**22**	**28**	**24**	**28**	**26**

Table 4: Results of Antifungal Activity

Compounds	µg/ml	*Aspergillus niger*	*Aspergillus flavus*	*Candida albicans*	*Fusarium oxysporium*
IV a	10	10	14	17	11
IV b	10	12	15	16	13
IV c	10	16	11	**19**	**18**
IV d	10	**18**	**17**	**21**	**18**
Fluconazole	10	**27**	**26**	**29**	**24**

ACKNOWLEDGEMENT

The authors are thankful to University College of Pharmaceutical Sciences, Kakatiya University, Warangal, and Andhra Pradesh for providing all the facilities and Heads of R and D institute, Vijayawada for providing the spectral data.

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