www.ijrps.pharmascope.org

ISSN: 0975-7538
Research Article

Eco-benign mediated versatile synthesis of newer quinazolin-4- (3H)-one clubbed isatin derivatives as potent antimicrobial agents

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ABSTRACT

A series of synthons consisting of a heterocyclic core flanked by two basic functionalities isatin and quinazolin-4-(3H)-one were synthesized using environmentally benign procedure and screened for *in vitro* antimicrobial activity. Neat reactants on subjecting to microwave irradiation gave the target products more quickly and in better yields. Benzoylation of anthranilic acid afforded the 2-phenyl-4H-benzo-(1,3)-oxazin-4-one **I**. The latter undergoes condensation with urea resulted in the formation of 4-oxo-2- phenyl quinazolin-4-(3H)-carboxamide **II**, which further undergoes condensation with isatin yielded the corresponding 4-oxo-N-(2-oxindolin-3-ylidene)-2-phenylquinazolin-4-(3H)-carboxamide **III**. This synthesized scaffolds were reacted under mannich condition to get the corresponding mannich bases of N-(1-substituted-2-oxoindolin-3-ylidene)-4-oxo-2-phenyl - quinazolin-4-(3H)carboxamide **IVa-IVf**. The chemical structures of all these title compounds have been confirmed by IR, ^{1}HNMR and mass spectral studies. Significant antimicrobial activities were observed for some members of the series.

Keywords: Synthons; mannich bases; spectral studies; in vitro antimicrobial activity.

INTRODUCTION

The quinazolinone structural motifs have attracted a great deal of interest due to their ready accessibility, diverse chemical reactivity and wide gamut of biological activities like anti -inflammatory (Ashok Kumar et al, 2009) antimalarial (A. Mishra et al, 2009), anthelmintic (Rajiv Dahiya et al, 2008), muscle relaxant (S. Buyuktimkin et al, 2006), antihyperlipidemic (Fawzia M Refaie et al, 2005), antitubercular (P.Y. Shirodkar et al, 1998) antimicrobial (AAF Wasfy, 2003) and hypotensive (Ashok Kumar et al, 2003) activities. The chemical versatility of isatin (2,3-indolinone) derivative has led to their extensive use as synthons for the preparation of many biologically active compounds (Surendranath Pandeya et al, 2006). A number of synthetic isatin derivatives serve both as biomimetic and reactive pharmacophores with profound pharmacological properties including anticonvulsant (Surendranath pandeya et al, 2005), antibacterial, antifungal (Surendranath Pandeya et al, 1999), anti-HIV (Surendranath pandeya et al, 1997), anti-viral (D.J.Bauer et al, 1960), antitubercular (Tarek Aboul Fadl et al, 2003), antihypertensive (B.A. Arinberg et al, 1989) and anti-histaminic (M.Sarangapani et al, 1997) activities. Substituted isatin-N-Mannich base derivatives were reported to possess both antibacterial and antifungal properties. As they are endowed with manifold biological activities associated with the isatin and quinazolinone derivatives, significant attention is paid on the annulation of these moieties in scaffolds could led to discovery of new therapeutic drug candidate. Recapitulation of literature reveals the synthesis of these compounds using conventional techniques is found to be time consuming.

The exploitation of microwaves for assisting different organic reactions has blossomed into an important tool in synthetic organic chemistry. Due to the timeless, ease of workability and eco-friendliness, microwaves provide an alternative to environmentally unacceptable procedures (Ashima Singh et al, 2009). Microwave energy offers numerous benefits performing synthesis including increased reaction rates, yield enhancements and cleaner chemistries (Khalid Mohammed Khan et al, 2004). Due to greater selectivity, rapid transfer of energy, significant practical simplicity and pure product, microwave - assisted reactions have greater advantageous over conventional homogenous methods. (Vetrivel Nadaraj et al, 2008). However the high cost of most conventional methods and their toxicity prompted us to explore other green processes. Hence, we now report an efficient microwave assisted synthesis of hitherto unreported quinazolin-4-(3H)-one coupled isatin derivatives and evaluation of antimicrobial activities of the title compounds.

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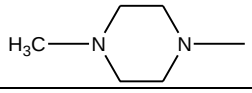
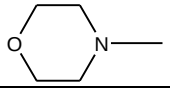
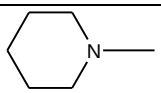
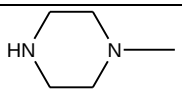
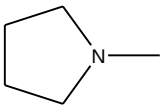
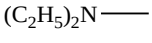
Received on: 26-03-2010
Revised on: 03-04-2010
Accepted on: 05-04-2010

Table 1: Physico chemical data of title compounds (IVa - IVf)

Compound Code	R	Molecular Formula	Molecular weight	R_f Value	Melting point (^{o}c)	Percentage yield (%)
IV a		$C_{29}H_{26}N_6O_3$	506.56	0.72	242.246	86
IV b		$C_{28}H_{23}N_5O_4$	493.51	0.64	252-255	82
IV c		$C_{29}H_{25}N_5O_3$	491.54	0.84	228-231	85
IV d		$C_{28}H_{24}N_6O_3$	492.53	0.69	262-265	78
IV e		$C_{28}H_{23}N_5O_3$	477.51	0.76	272-274	78
IV f		$C_{28}H_{25}N_5O_3$	479.53	0.75	236-238	90

MATERIALS AND METHODS

All reagents used were of analytical grade AR and purchased from Sigma Aldrich Chemical Ltd. Melting points of the target compounds were determined using Veego Digital VMP-D melting point apparatus and are uncorrected. Infra red spectra (cm^{-1}) were recorded on Shimadzu - 8201 spectrometer as pellets on KBr discs. The ^{1}HNMR (400 MHz) spectra were recorded on Bruker Avance-II Spectrometer in DMSO-d_6 using TMS as an internal reference (chemical shifts in δ ppm) unless otherwise stated. The splitting patterns are designated as follows: s, singlet, d, doublet, t, triplet, m, multiplet. Mass spectra were recorded on shimadzu LCMS- SL 2010A (70 ev) mass spectrometer. The reactions were monitored by thin layer chromatography (TLC) using precoated silica gel G plates of E-Merck. The spots were developed in iodine chamber and visualized under ultraviolet lamp. The microwave-irradiated reactions were performed in CATALYST-2R scientific microwave oven.

GENERAL PROCEDURES

Synthesis of 2-phenyl -4H-benzo-[1, 3]-oxazin-4-one (I)

0.05 mole of anthranilic acid was dissolved in 30ml of pyridine and cooled to 0^{o}c.To this reaction mixture, 0.04 mole of benzoyl chloride was added and stirred for 30 minutes at room temperature by using magnetic stirrer. Further it was diluted with 50ml of water and neutralized with 50ml of 5% sodium bicarbonate solution. The resultant mixture was washed with distilled water and the solid mass was filtered, dried and recrystallised from hot ethanol. The physico-chemical data and melting point of the synthesized products were in full agreement with that of reported method.

Synthesis of 4-oxo - 2-phenyl quinazolin-4-(3H)-carboxamide (II)

0.01 mole of 2-phenyl-4H-benzo [1, 3]-oxazin-4-one **(I)** was dissolved in 5ml of methanol. To this 0.01 mole of urea was added and stirred. Then the resulting mixture was subjected to microwave irradiation for a time period of 3 minutes at an output of 160 watts under neat condition. After the completion of reaction, the precipitate formed was filtered and recrystallised using hot ethanol.

Synthesis of 4-oxo-N-(2-oxindolin-3-ylidene)-2-phenyl quinazolin-4-(3H)-carboxamide (III)

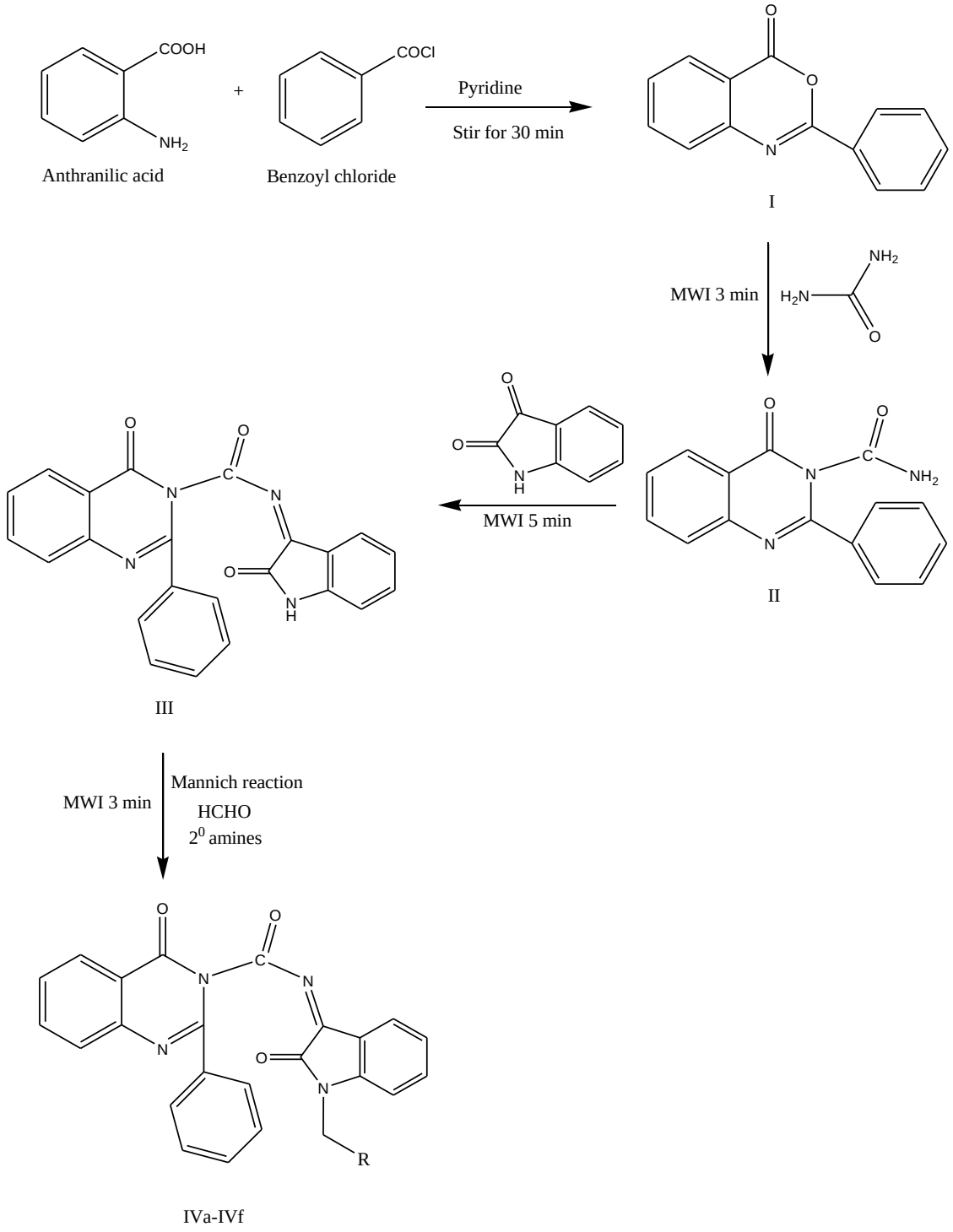
0.01 mole of 4-oxo-2- phenyl quinazolin-4-(3H)-carboxamide **(II)** was dissolved in 5ml of methanol. To the methanolic solution, 0.01 mole of isatin was added and stirred well. The reaction mixture was irradiated using microwaves for 5 minutes. The afforded crude product was separated and recrystallised from hot ethanol.

Synthesis of N-(1-substituted-2-oxindolin-3-ylidene)-4-oxo-2-phenyl quinazolin-4-(3H)- carboxamide (IVa-IVf)

To a methanolic solution of 4-oxo-N-(2-oxindolin-3-ylidene)-2-phenyl quinazolin-4-(3H) carboxamide (**III**), 0.01 mole of formaldehyde and 0.01 mole of different substituted secondary amines was added and stirred well. The whole content was irradiated under microwaves for 3 minutes and cooled to room temperature. The physico chemical data of title compounds (**IVa-IVf**) were depicted in table 1.

1-[(4-methyl piperazinyl) methyl]-2-oxo-indolin-3-ylidene)-4-oxo-2-phenyl quinazolin-4-(3H)-carboxamide (IVa).

Scheme



Yield 86%, m.p 242-246^{o}C, IR (KBr, cm^{-1}) 3048 (Ar-CH str.), 1690 (C=O str. of 4 (3H) quinazolinone ring), 1576 (C=N str.), 1653 (C=O, amide), 1610 (C=N str.of isatin ring), 1734 (C=O str.of isatin ring), 1452 (-CH_2 str.); ^{1}HNMR (DMSO -d_6): δ ppm 7.3-7.8 (m, 4H, Ar-H of (3H) quinazolinone ring), 7.3 -7.6 (m, 5H, Ar-H of phenyl ring of quinazolinone), 7.0 - 7.7 (m, 4H, Ar-H of isatin ring), 4.1 (s, 2H, -CH_2), 2.4 (m, 8H, $(CH_2)_4$ of piperazine ring). M/Z = 507 (M+1).

(1-morpholino methyl)-2-oxo-indolin-3-ylidene)-4-oxo-2-phenyl quinazolin-4-(3H)- carboxamide (IVb).

Yield 82%, m.p 252-255^{o}C, IR (KBr, cm^{-1}) 3046 (Ar-CH str.), 1696 (C=O str. of 4 (3H) quinazolinone ring), 1574 (C=N str.), 1658 (C=O, amide), 1614 (C=N str.of isatin ring), 1737 (C=O str.of isatin ring), 1450 (-CH_2 str.); ^{1}HNMR (DMSO -d_6): δ ppm 7.2-7.7 (m, 4H, Ar-H of (3H) quinazolinone ring), 7.2 -7.8 (m, 5H, Ar-H of phenyl ring of quinazolinone), 7 - 7.4 (m, 4H, Ar-H of isatin ring),

4.2 (s, 2H, -CH_2), 3.6 (m, 8H, $(CH_2)_4$ of morpholine ring). M/Z = 494 (M+1).

(1-piperidinyl methyl) -2-oxo - indolin - 3 ylidene) -4-oxo - 2- phenyl quinazolin-4-(3H)- carboxamide. (IVc)

Yield 85%, m.p 288-231^oC, IR (KBr, cm^{-1}) 3062 (Ar-CH str.), 1670 (C=O str. of 4 (3H) quinazolinone ring), 1592 (C=N str.), 1664 (C=O, amide), 1614 (C=N str.of isatin ring), 1732 (C=O str.of isatin ring), 1452 (-CH_2 str.); ^{1}HNMR (DMSO -d_6): δ ppm 7.4-7.8 (m, 4H, Ar-H of (3H) quinazolinone ring), 7.2 -7.4 (m, 5H, Ar-H of phenyl ring of quinazolinone), 7.0 - 7.6 (m, 4H, Ar-H of isatin ring), 4.2 (s, 2H, -CH_2), 2.2 (m, 10H, $(CH_2)_5$ of piperidine ring). M/Z = 492 (M+1).

(1-piperazinyl methyl) -2-oxo - indolin - 3 ylidene) -4-oxo - 2- phenyl quinazolin –4-(3H)- carboxamide. (IVd)

Yield 78%, m.p 262-265^oC, IR (KBr, cm^{-1}) 3050 (Ar-CH str.), 1682 (C=O str. of 4 (3H) quinazolinone ring), 1584 (C=N str.), 1664 (C=O, amide), 1614 (C=N str.of isatin ring), 1742 (C=O str.of isatin ring), 1462 (-CH_2 str.); ^{1}HNMR (DMSO -d_6): δ ppm 7.3-7.8 (m, 4H, Ar-H of (3H) quinazolinone ring), 7.2 -7.5 (m-, 5H, Ar-H of phenyl ring of quinazolinone), 7.0 - 7.4 (m, 4H, Ar-H of isatin ring), 4.3 (s, 2H, -CH_2), 2.4 (m, 8H, $(CH_2)_4$ of piperizine ring), 2.0(s,1H, -NH of piperazine ring). M/Z = 493 (M+1).

(1-pyrrolidinyl methyl)-2-oxo-indolin-3-ylidene)-4-oxo-2-phenylquinazolin-4-(3H)- carboxamide. (IVe)

Yield 78%, m.p 272-274^oC, IR (KBr, cm^{-1}) 3058 (Ar-CH str.), 1664 (C=O str. of 4 (3H) quinazolinone ring), 1594 (C=N str.), 1658 (C=O, amide), 1634 (C=N str.of isatin ring), 1742 (C=O str.of isatin ring), 1456 (-CH_2 str.); ^{1}HNMR (DMSO -d_6): δ ppm 7.4-7.8 (m, 4H, Ar-H of (3H) quinazolinone ring), 7.2 -7.6 (m, 5H, Ar-H of phenyl ring of quinazolinone), 7.0 - 7.5 (m, 4H, Ar-H of isatin ring), 4.2 (s, 2H, -CH_2), 2.7 (m, 8H, $(CH_2)_4$ of pyrolidine ring), M/Z = 478 (M+1).

(1-diethyl amino) methyl-2-oxo-indolin-3-ylidene)-4-oxo-2-phenyl quinazolin-4-(3H)- carboxamide. (IVf)

Yield 90%, m.p 236-238^oC, IR (KBr, cm^{-1}) 3038 (Ar-CH str.), 1682 (C=O str. of 4 (3H) quinazolinone ring), 1572 (C=N str.), 1658 (C=O, amide), 1624 (C=N str.of isatin ring), 1738 (C=O str.of isatin ring), 1448 (-CH_2 str.); ^{1}HNMR (DMSO -d_6): δ ppm 7.2-7.6 (m, 4H, Ar-H of (3H) quinazolinone ring), 7.2 -8.2 (m, 5H, Ar-H of phenyl ring of quinazolinone), 7.2 - 7.4 (m, 4H, Ar-H of isatin ring), 4.0 (s, 2H, -CH_2), 1.4 (m, 8H, $(CH_2)_2$), 0.9 (m, 6H, $(CH_3)_2$). M/Z = 480 (M+1).

Antimicrobial Activity

The antimicrobial activity was assayed by using cup-plate diffusion method (M.N. Ghosh, 2005) by measuring the inhibition zones in mm. Compounds **(IVa-IVf)** were screened *in vitro* for their antimicrobial activity against a variety of bacterial strains such as *Staphylococcus aureus, Klebsiella pneumoniae, Escherichia coli* and *Pseudomonas aeruginosa* and fungal strains such as *Aspergillus niger* and *Candida albicans* at different concentrations of 100, 200, 300mg/ml. Known antibiotics like Ofloxacin and Griseofulvin were used as standard for comparison .

Antibacterial Activity

The purified title products were screened for its antibacterial activity. The nutrient agar broth prepared by the usual method (M.J.Pelczar, 1993) was inoculated especially with 0.5ml for 24 hours old subculture of all the mentioned bacterial strains were taken in a separate conical flask at 40-50^oC and mixed well by gentle shaking. About 25ml of the contents of the flasks were poured and evenly spread in a petridish (13cm in diameter) and allowed to set for 2 hours. The cups (10mm in diameter) were formed by the help of borer in agar medium and filled with synthesized samples dissolved in dimethyl formamide(DMF). The plates were incubated at 37^oC for 24 hours and control was also maintained in similar manner. The zone of inhibition of the bacterial growth is measured in mm diameter and is recorded in table 2.

Antifungal Activity

Aspergillus niger and *Candida albicans* were employed for testing fungicidal activity using cup plate method (Satish Gupte, 1995). The cultures were maintained on Sabouraud's agar slants. Sterilized Sabouraud's agar medium was inoculated with 72 hours old suspension of fungal spores in a separate flask. About 25ml of the inoculated medium was evenly spread in a sterilized petridish and allowed to settle down for 2 hours. The cups (10mm in diameter) were punched in petridish and loaded with sample solution in DMF. The plates were incubated at room temperature (30^oC) for 48 hours. After the completion of the incubation period, the zone of inhibition of growth of compounds **(IVa-IVf)** in the form of diameter in mm were measured. Along the test solution in each petridish, one cup was filled with solvent which acted as control. The antifungal activity of compound was compared with known standard drugs mentioned above, which are recorded in table 2.

RESULTS AND DISCUSSION

The amino alkylation of aromatic substrates by the mannich reaction is of considerable importance for the synthesis and modification of biologically active compounds. The synthesis of target compound was accomplished as shown in the scheme. Anthranilic acid on benzoylation gave the known 2-phenyl -4H-benzo-(1,3)-oxazin-4-one **(I)**. Subsequent condensation reaction with urea resulted in the facile synthesis of 4-oxo-2-phenyl quinazolin –4-(3H)-carboxamide **(II)**. The latter undergoes further condensation with isatin furnished the formation of 4-oxo-N-(2-oxindolin-3-ylidene)-2-phenyl quinazolin-4-(3H)-carboxamide **(III)**. Finally aminomethylation reaction was performed to

Table 2: *In vitro* antimicrobial profile of the title compounds (IVa-IVf)

Compounds	Concentration (mg/ml)	Antibacterial activity zone of inhibition (mm)				Antifungal activity zone of inhibition (mm)	
		S.aureus	*K.pneumoniae*	*E.coli*	*P.aeruginosa*	*A.niger*	*C.albicans*
IVa	100	13	13	13	13	24	25
	200	15	14	15	14	27	28
	300	18	17	17	16	29	31
IVb	100	16	17	15	16	24	26
	200	18	20	19	19	27	28
	300	20	22	21	23	28	30
IVc	100	18	17	16	17	24	27
	200	20	19	18	23	26	29
	300	23	22	21	25	29	30
IVd	100	13	13	15	14	15	15
	200	17	15	17	16	16	17
	300	18	17	19	18	18	19
IVe	100	15	16	13	13	18	18
	200	16	18	15	15	24	20
	300	17	20	18	17	25	22
IVf	100	15	16	16	15	22	24
	200	18	18	17	17	25	26
	300	21	20	18	19	26	28
Ofloxacin	100	40	37	36	35	-	-
	200	44	39	38	37	-	-
	300	46	41	40	38	-	-
Griseofulvin	100	-	-	-	-	34	37
	200	-	-	-	-	36	39
	300	-	-	-	-	37	40

afford the desired compounds **(IVa-IVf)**. All the reactions proceeded smoothly under microwave irradiation facilitated the formation of products in short time with high yield.

The infrared spectroscopic investigation of all the compounds **(IVa - IVf)** showed a sharp peak at 1690 cm^{-1} attributed to C=O stretching of 4 (3H) quinazolinone ring and band at 1734 cm^{-1} revealed the appearance of C=O stretching of isatin. The formation of mannich bases is indicated by the presence of -N-CH_2 peak at 1452 cm^{-1}. All these characteristic IR bands confirmed the formation of final compounds.

The ^{1}HNMR spectrum showed a resonate singlet at δ 4.1 ppm due to the characteristics of -CH_2 proton. The multiplet signals at δ 7.2 - 8.0 attributed to the aromatic ring protons. Molecular ion peak of the final compounds were found to be in correlation with the expected structure. Thin layer chromatography was run throughout the reaction to optimize the reaction completion.

The title compounds **(IVa-IVf)** were evaluated for *in vitro* antimicrobial activity against pathogenic microorganisms by cup plate diffusion method. Most of the compounds exhibited mild to moderate antimicrobial activity against all the microbes tested. The results reveals that among the tested compounds **IVb**, **IVc**, **IVd**, **IVf** were found to have better activity, whereas the remaining compounds **IVa**, **IVe** were found to be less active. Antifungal screening revealed that the test compounds **IVa**, **IVb**, **IVd**, **IVe** and **IVf** showed better activity as compared to standard drug Griseofulvin.

CONCLUSION

We have synthesized successfully a series of isatin installed quinazolinone hybrid molecules with the aid of green chemistry. The desired product formed was fast, eco-friendly, cheaper, high yield and easy to handle. The constitution of all the title compounds assigned on the basis of IR, ^{1}HNMR and mass spectral data were found to be in correlation with the desired structure. The present results are worth noticing in the case of antimicrobial activity of the tested compounds. It can also be stated that they are promising new antimicrobial agents in treating microbial infections.

ACKNOWLEDGEMENTS

Authors are grateful to Dr.R.ShivaKumar, Provicechancellor, SRM University and Dr.K.S.Lakshmi, Dean, College of Pharmacy, SRM University, Kattankulathur for providing facilities to carry out this work.

REFERENCES

AAF Wasfy, Synthesis and antimicrobial evaluation of some 2,2-disubstituted-3,3- biquinazolin-4-(3H)-ones. *Indian Journal of Chemistry, 2003, 3102-3107.*

Arinberg B.A., Safronova I.E., Mazhillis L.F., Effect of certain benzistain on oxidative determination of Tyramine-Hcl. *Pharmaceutical Chemistry Journal, 1989, 633-635.*

Ashima singh, ML Sharma, Jasvinder singh, Synthesis of 2,6-dimethyl-6-hydroxy-2,7- octadienoic acid, its methyl ester and 2,6-dimethyl octa -2,7-diene-1,6-diol over solid support using microwave. *Indian Journal of Chemistry, 2009, 452-454.*

Ashok Kumar, Chatrasal singh Rajput, Synthesis and anti-inflammatory activity of newer quinazolin-4-one derivatives. *European Journal of Medicinal chemistry, 2009, 83-90.*

Ashok kumar, Mirdula Tyagi, Srivastava V.K.,Newer Potential quinazolinones as hypotensive agents. *Indian Journal of Chemistry, 2003, 2142-2145*.

Bauer D.J., Sadler P.W., The structure-activity relationship of the antiviral chemotherapeutic activity of isatin -β -thio semicarbazone. *Brit. J. Pharmocol., 1960, 101.*

Buyuktimkin S., Ekinici A.C., Pharmacological studies on quarternized–4-(3H)- quinazolinones. *Journal of Pharmaceutical sciences, 2006, 1092 – 1094.*

Fawzia M Refaie, Amry Esmat, The antihyperlipidemic activities of 4-(3H)-quinazolinones and two halogented derivatives in rats. *Lipid in health and disease, 2005, 22.*

Ghosh M.N., Fundamentals of Experimental Pharmacology, S.K.Ghosh publishing house, 2nd edn, kolkatta, 2005, 212-215.

Khalid Mohammed Khan, Zia-Ullah, Mubeen Rani, Atta -Ur-Rahman, Microwave assisted synthesis of 2,5-disubstituted 1,3,4- oxadiazoles. *Letters in Organic Chemistry, 2004, 50-52*.

Pelczar M.J., Chan E.C.S., Krig N.R., Text book of Microbiology, MC Graw- Hill publication, 5th edn, Newyork, 1993, 504-508.

Rajiv dahiya, Anilkumar, Synthesis and biological activity of peptide derivatives of Iodoquinazolonones. *Molecules, 2008, 958-976*.

Sarangapani M., Reddy V.M., Pharmacological screening of isatin - (N-(2-alkyl benzoxazole -5- carbonyl) hydrazones. *Indian Journal of Pharmaceutical Sciences, 1997, 105-109.*

Satish Gupte, Text book of Medical Microbiology Jaypee brother Medical publishers, 6th edn, New Delhi, 1995, 82-87.

Shirodkar P.Y., Meghana M.V., Synthesis and Pharmacological activities of 6-bromo, -3-N - aryl amino methyl, 1, 2, 3, 4 tetrahydro -4-oxo-2-thioquinazolines. *Indian Drugs, 1998, 597-599.*

Surendranath Pandeya, Raja A.S., Nath G., Synthesis and antimicrobial evaluation of some 4 or 6- chloro isatin derivatives. *Indian Journal of Chemistry, 2006, 494-499.*

Surendranath Pandeya, Siva Kumar Smitha, Mayank Jyoti, Seshaiah Krishnan, Biological activity of isatin and its derivatives*. Acta-pharma., 2005, 27-46.*

Surendranath pandeya, Sriram D., Nath G., Ede clercq, Synthesis and anti-HIV activity of Schiff's and Mannich base derivatives from isatin with 3-amino -2-methyl mercapto quinazolin –4-(3H)-one. *Pharmaceutica Acta Helvetiae, 1997, 11-17.*

Surendranath Pandeya, Sriram D., Nath G., Ede clercq, Synthesis, antibacterial and antifungal activities of Schiff's and Mannich base derivatives from isatin with N-(4-(4'- chlorophenyl) thiazol -2-yl)-thio semicarbazide. *European Journal of Pharmaceutical Sciences, 1999, 25-31.*

Tarek Aboul - Fadl, Faraqany abdel - Hamid, Ehsan abdel, saboor hassan, Synthesis and antitubercular activity of some Schiff's base derivatives from 1-alkyl isatin and isonicotinic acid hydrazide. *Archives of pharmacology Reasearch, 2003, 778-784.*

Vetrivel Nadaraj, Senniappan Thamarai Selvi, Sellappan Mohan Microwave – induced synthesis and antimicrobial activities of 7, 10, 11, 12 - tetrahydo benzo (c) acridin –8- (9H)- one derivatives. *European Journal of Medicinal Chemistry, 2009, 976-980.*