Synthesis and Characterization of Some Quinazoline Derivatives as Potential Antimicrobial Agents under Microwave Irradiation

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Under the framework of green chemistry, an efficient and extremely fast procedure for the synthesis of **5a-h** through four-step procedure starting from 2-arylidenetetralin-1-one **1a-d** under microwave irradiation is described. A considerable increase in the reaction rate has been observed with better yield. The structures of the synthesized compounds have been characterized on the basis of their elemental analysis and spectral data. Synthesized compounds **5a-h** was evaluated for their antimicrobial activity. Some of the compounds exhibited appreciable activity.

Key Words : Tetralone, Chalcone, Thiazolidinone, Isoxalzoline, Microwave irradiation

Introduction

In recent years thiazolidinone derivatives have gained unique importance due to broad spectrum of pharmacological activities[1,2] which are reflected by their use as analgesic,[3] antifungal,[4] antiinflamatory[5,6] and anti HIV activity.[7] Some of thiazolidinone derivatives exhibited resistance against some potentially fatal disease such as cancer,[8,9] tuberculosis[10] etc. The importance of fused isoxazole, common sources for the development of new therapeutic agents,[11,12] is well known. Quinazoline is a big family of heterocyclic compounds which has shown broad variety of biological activity profiles,[13,14] such as analgesic, narcotic, diuretic, antihypertensive, antimalarial, sedative, hypoglycemic, antibiotic, antitumoral and many others. These examples clearly demonstrate the remarkable potential of quinazoline derivatives as a source of useful pharmacophore for new drug evolution. As our interest in "search for bioactive heterocycles," we sought an unexplored, synthetically accessible heterocyclic template (quinazoline) capable of bearing some potential pharmacophores to elicit and enhance the inherent biological activity. Thus either synthesis of this heterocyclic nucleus or its incorporation into some established pharmacophores like thiazolidinone[15] and isoxazole,[16] is of continuing interest and has been the aim of the present investigation. In view of the high biological activity of compounds related to quinazoline in particular and thiazolidinone and isoxazole in general we became interested in devising eco-friendly synthetic methodologies for the preparation of large quantities for pharmacological evolution and other purposes. Microwave induced organic transformations[17,18] stands among the alternative routes proposed during the last decade or so due to various reasons like higher yields in shortest possible time and above all eco-friendliness. This paper describes an efficient and operationally simple method for the synthesis of title compounds under microwave irradiation versus conventional thermal cyclisation for comparative purpose.

Results and Discussion

The high throughput afforded by microwave technology is exemplified by the successful synthesis of the targeted compounds by the installation of various moieties in one molecule through a multistep reaction procedure. In order to achieve our objective 2-arylidenetetralin-1-ones **1a-d**, obtained by the condensation of α-tetralone with appropriate aromatic aldehydes, were treated with thiourea in alkaline medium yielded 4-aryl-3,4,5,6-tetrahydrobenzo[h]quinazolin-2(1H)-thiones **2a-d** in good yield. Compound **2a** showed characteristic IR absorption band in the regions 3333 cm^{-1} (N-H), 1220 cm^{-1} (C=S) and 750 cm^{-1} (C-Cl). Its ^{1}H NMR spectrum exhibited two singlet at δ 5.05 (-CH_a) and δ 6.40 (N-H). Furthermore it showed two characteristic quinazoline triplets (J = 8.0 Hz) at δ 2.60 and at δ 2.15. The thiones **2a-d** on reaction with chloroacetic acid and subsequent cyclisation of the intermediates *in situ* was likely to give 5-aryl-2,3,6,7-tetrahydro-3-oxo-5H-thiazolo[2,3-b]benzo[h]quinazolines **3a-d**. IR spectrum of compound **3a** was in well agreement to the assigned structure showing the absence of band at 3333 cm^{-1} of N-H str. and at 1220 cm^{-1} of (C=S) and showing the band at 1710 cm^{-1} (C=O thiazolidinone ring) and 701 cm^{-1} (C-S-C). Another possible isomeric structure **6a-d** could be proposed for the prepared compounds. However the structures **6a-d** can be readily discarded on the basis of the fact that in benzoquinazoline **2a-d**, the most nucleophile site is the cyclic secondary 'N' atom at position-3. Expansion of the ^{1}H NMR spectrum further confirmed the structure of these compounds that gave an interesting feature of H_a proton. The H_a proton in **2a** resonated at δ 5.05 where as cyclic product obtained from **2a** gave the signal for same H_a proton at δ 5.70. It confirms the proposed structure **3a** in which the H_a proton was de-shielded by the carbonyl group of the thiazolidinone ring and appeared downfield as compared to the same proton in **2a**. Thiazolidinone derivatives **3a-d** was condensed with aromatic aldehydes to give arylidene derivatives **4a-h** which were characterized by IR and

^{1}H NMR spectral data. The IR spectrum of compounds **4a** showed the absence of carbonyl absorption of thiazolidinone at 1710 cm^{-1} and the presence of chalcone carbonyl, band (C=C-C=O) at **1670** cm^{-1}. Its ^{1}H NMR spectrum displayed new singlet at δ 6.60 attribute to chalcone moiety (=CH$_b$ proton). The arylidene compounds **4a-h** on reaction with hydroxylamine hydrochloride afforded their respective *in situ* oxidized products **5a-h**. The disappearance of the carbonyl str. at **1670** cm^{-1} and appearance of band at 1075 cm^{-1} (C-O) and 900 cm^{-1} (N-O) in IR spectrum for **5a** confirms the installation of isoxazole moieties in **4a**. The substrate **4** having a –C=C-C=O- (α-, β-unsaturated carbon-

Table 1. Characterization data of synthesized compounds

Compd.	m.p.(C)	Yield (%)		Molecular Formula (M.W.)	Calculated/Found (%)			
		Classical	Microwave		C	H	N	S
2a	210 (EtOH)	63	85	$C_{18}H_{15}N_2SCl$ (326)	66.25 65.92	4.60 4.49	8.58 8.52	9.81 9.77
2b	185 (EtOH)	55	90	$C_{18}H_{15}N_2SF$ (310)	69.67 69.40	4.83 4.14	9.03 9.02	10.32 10.29
2c	156 (EtOH)	52	75	$C_{19}H_{18}N_2SO$ (322)	70.80 70.52	5.59 5.10	8.69 8.64	9.93 9.88
2d	225 (EtOH)	51	67	$C_{18}H_{16}N_2SCl$ (292)	73.97 73.67	5.47 5.30	9.58 9.52	10.95 10.90
3a	175 (EtOH)	45	86	$C_{20}H_{15}N_2SOCl$ (366)	65.57 65.64	4.09 3.84	7.65 7.63	8.74 8.77
3b	190 (EtOH)	63	82	$C_{20}H_{15}N_2SOF$ (350	68.57 68.42	4.28 4.02	8.00 8.00	9.14 9.10
3c	238 (EtOH)	58	83	$C_{21}H_{18}N_2SO_2$ (362)	69.61 69.76	5.24 4.72	7.73 7.71	8.83 8.77
3d	184 (EtOH)	50	79	$C_{20}H_{15}N_2SO$ (331)	72.28 72.26	4.51 4.44	8.43 8.40	9.63 9.62
4a	178 ($CHCl_3$)	61	81	$C_{27}H_{18}N_2SOCl_2$ (489)	66.25 66.20	3.68 3.29	5.72 5.71	6.54 6.52
4b	245 ($CHCl_3$)	57	91	$C_{27}H_{18}N_2SOClF$ (472)	68.64 68.21	3.81 3.39	5.93 5.91	6.77 6.72
4c	215 ($CHCl_3$)	54	88	$C_{28}H_{21}N_2SO_2Cl$ (484)	69.42 69.31	3.71 3.68	5.78 5.71	6.61 6.53
4d	280 ($CHCl_3$)	49	79	$C_{27}H_{19}N_2SOCl$ (454)	74.00 71.60	4.18 3.76	6.16 6.13	7.04 7.02
4e	165 ($CHCl_3$)	52	83	$C_{27}H_{18}N_2SOClF$ (472)	68.64 68.55	3.81 3.40	5.93 5.90	6.77 6.70
4f	260 ($CHCl_3$)	62	85	$C_{27}H_{18}N_2SOF_2$ (456)	71.05 71.03	3.94 3.54	6.14 6.14	7.01 7.00
4g	148 ($CHCl_3$)	56	89	$C_{28}H_{21}N_2SO_2F$ (468)	71.79 71.06	4.48 4.05	5.98 5.93	6.83 6.80
4h	213 ($CHCl_3$)	61	84	$C_{27}H_{19}N_2SOF$ (438)	73.97 73.26	4.10 3.91	6.39 6.38	7.30 7.20
5a	225 (EtOH)	50	90	$C_{27}H_{19}N_3SOCl_2$ (504)	64.28 64.20	3.76 3.20	8.33 8.30	6.34 6.31
5b	210 (EtOH)	45	88	$C_{27}H_{19}N_3SOClF$ (487)	66.52 66.50	3.90 3.30	8.62 8.64	6.57 6.52
5c	192 (EtOH)	60	85	$C_{28}H_{22}N_3SO_2Cl$ (499)	67.33 66.60	4.40 3.83	8.41 8.12	6.41 6.32
5d	205 (EtOH)	51	87	$C_{27}H_{20}N_3SOCl$ (469)	69.08 69.00	4.26 3.63	8.95 8.93	6.82 6.81
5e	188 (EtOH)	54	92	$C_{27}H_{19}N_3SOClF$ (487)	66.52 66.40	3.90 3.29	8.62 8.62	6.57 6.54
5f	218 (EtOH)	52	88	$C_{27}H_{19}N_3SOF_2$ (471)	68.78 68.20	4.03 3.41	8.91 8.90	6.79 6.72
5g	220 (EtOH)	60	89	$C_{28}H_{22}N_3SO_2F$ (483)	69.56 69.50	4.55 3.97	8.69 8.60	6.62 6.60
5h	198 (EtOH)	55	90	$C_{27}H_{20}N_3SOF$ (453)	71.52 71.40	4.41 3.77	9.27 9.20	7.06 7.01

Table 2. Spectral data of synthesized compounds

Comp. No.	Spectra
2a	IR: υ = 3333 (N-H), 3080 (Ar-H), 1220 (C=S), 750 (C-Cl) cm^{-1}. ^1H NMR (DMSO-d_6): δ= 6.85-7.40 (m, 8H, Ar-H), 6.40 (s, 2H, NH), 5.05 (s, 1H, CH_a), 2.60 (t, 2H, C_7-CH_2), 2.15 (t, 2H, C_6-CH_2) ppm
2b	IR: υ = 3320 (N-H), 3072 (Ar-H), 1218 (C=S), 1110 (C-F) cm^{-1} . ^1H NMR (DMSO-d_6): δ= 6.80-7.80 (m, 8H, Ar-H), 6.25 (s, 2H, NH), 4.94 (s, 1H, -CH_a), 2.72 (t, 2H, C_7-CH_2), 2.10 (t, 2H, C_6-CH_2) ppm
2c	IR: υ = 3310 (N-H), 3070 (Ar-H), 1209 (C=S) 1080 (C-O) cm^{-1}. ^1H NMR (DMSO-d_6): δ= 6.9-7.6 (m, 8H, Ar-H), 6.3 (s, 2H, NH), 4.98 (s, 1H, -CH_a), 3.5 (s, 3H, -OCH_3), 2.68 (t, 2H, -C_7-CH_2), 2.14 (t, 2H, C_6-CH_2) ppm
2d	IR: υ = 3318 (N-H), 3078 (Ar-H), 1209 (C=S) cm^{-1}. ^1H NMR (DMSO-d_6): δ= 6.74-7.80 (m, 9H, Ar-H). 6.15 (s, 2H, NH), 5.00 (s, 1H, CH_a), 2.64 (t, 2H, C_7-CH_2), 2.08 (t, 2H, C_6-CH_2) ppm
3a	IR: υ = 3048 (Ar-H), 2887 (CH_2), 1710 (thiazolidinone C=O), 1628 (C=N), 750 (C-Cl), 701 (C-S) cm^{-1}. ^1H NMR (DMSO-d_6): δ= 6.87-7.92 (m, 8H, Ar-H), 5.70 (s, 1H, -CH_a), 4.20 (s, 2H, S-CH_2), 2.87 (t, 2H, C_7-CH_2), 2.30 (t, 2H, C_6-CH_2) ppm
3b	IR: υ = 3028 (Ar-H), 2872 (CH_2), 1698 (thiazolidinone C=O), 1620 (C=N), 1120 (C-F) cm^{-1}, 705 (C-S-C). ^1H NMR (DMSO-d_6): δ= 6.50-7.25 (m, 8H, Ar-H), 5.67 (s, 1H, -CH_a), 4.06 (s, 2H, S-CH_2) 705 (C-S-C), 2.81 (t, 2H, C_7-CH_2), 2.28 (t, 2H, C_6-CH_2) ppm
3c	IR: υ = 3060 (Ar-H), 2878 (-CH_2), 1705 (thiazolidinone-C=O), 1622 (C=N), 1080 (C-O) 703 (C-S-C) cm^{-1}. ^1H NMR (DMSO-d_6): δ= 7.05-7.92 (m, 8H, Ar-H), 5.73 (s, 1H, CH_a), 4.24 (s, 2H, S-CH_2), 3.52 (s, 3H, -OCH_3), 2.88 (t, 2H, C_7-CH_2), 2.34 (t, 2H, C_6-CH_2) ppm
3d	IR: υ = 3050 (Ar-H), 2890 (-CH_2), 1700 (thiazolidinone C=O), 1623 (C=N) 700 (C-S-C) cm^{-1}. ^1H NMR (DMSO-d_6): δ= 6.84-7.90 (m, 9H, Ar-H), 5.68 (s, 1H, CH_a), 4.09 (s, 2H, S-CH_2), 2.77 (t, 2H, C_7-CH_2), 2.27 (t, 2H, C_6-CH_2) ppm
4a	IR: υ = 3100 (Ar-H), 1670 (C=O), 1630 (C=N), 748 (C-Cl), 686 (C-S-C) cm^{-1}. ^1H NMR (DMSO-d_6): δ= 6.90-7.85 (m, 12H, Ar-H), 6.60 (s, 1H, CH_b), 5.70 (s, 1H, CH_a), 2.70 (t, 2H, C_7-CH_2), 2.10 (t, 2H, C_6-CH_2) ppm
4b	IR: υ = 3078 (Ar-H), 1668 (C=O), 1625 (C=N), 1180 (C-F), 745 (C-Cl), 684 (C-S-C), cm^{-1}. ^1H NMR (DMSO-d_6): δ= 6.90-7.85 (m, 12H, Ar-H), 6.52 (s, 1H, CH_b), 5.68 (s, 1H, CH_a), 2.65 (t, 2H, C_7-CH_2), 2.08 (t, 2H, C_6-CH_2) ppm
4c	IR: υ = 3050 (Ar-H), 1665 (C=N), 1075 (C=O), 748 (C-Cl), 680 (C-S-C) cm^{-1}. ^1H NMR (DMSO-d_6): δ= 6.76-7.81 (m, 12H, Ar-H), 6.50 (s, 1H, CH_b), 5.59 (s, 1H, CH_a), 3.82 (s, 3H, OCH_3), 2.64 (t, 2H, C_7-CH_2), 2.09 (t, 2H, C_6-CH_2) ppm
4d	IR: υ = 3072 (Ar-H), 1662 (C=O), 1620 (C=N), 745 (C-Cl), 678 (C-S-C) cm^{-1}. ^1H NMR (DMSO-d_6): δ= 6.71-7.50 (m, 12H, Ar-H), 6.42 (s, 1H, CH_b), 5.51 (s, 1H, CH_a), 2.60 (t, 2H, C_7-CH_2), 2.07 (t, 2H, C_6-CH_2) ppm
4e	IR: υ = 3068 (Ar-H), 1660 (C=O), 1622 (C=N), 1168 (C-F),746 (C-Cl), 672 (C-S-C) cm^{-1}. ^1H NMR (DMSO-d_6): δ= 6.62-7.42 (m, 12H, Ar-H), 6.48 (s, 1H, CH_b), 5.59 (s, 1H, CH_a), 2.63 (t, 2H, C_7-CH_2), 2.05 (t, 2H, C_6-CH_2) ppm
4f	IR: υ = 3075 (Ar-H), 1675 (C=O), 1634 (C=N), 1182 (C-F), 684 (C-S-C) cm^{-1}. ^1H NMR (DMSO-d_6): δ= 6.76-7.53 (m, 12H, Ar-H), 6.42 (s, 1H, CH_b), 5.52 (s, 1H, CH_a), 2.51 (t, 2H, C_7-CH_2), 2.00 (t, 2H, C_6-CH_2) ppm
4g	IR: υ = 3080 (Ar-H), 1670 (C=O), 1627 (C=N), 1180 (C-F), 1050 (C-O) cm^{-1}. ^1H NMR (DMSO-d_6): δ= 6.80-7.72 (m, 12H, Ar-H), 6.56 (s, 1H, CH_b), 5.72 (s, 1H, CH_a), 3.48 (s, 3H, -OCH_3), 2.68 (t, 2H, C_7-CH_2), 2.12 (t, 2H, C_6-CH_2) ppm
4h	IR: υ = 3072 (Ar-H), 1665 (C=O), 1620 (C=N), 1172 (C-F) cm^{-1}. ^1H NMR (DMSO-d_6): δ= 6.80-7.94 (m, 13H, Ar-H), 6.58 (s, 1H, CH_b), 5.64 (s, 1H, CH_a), 2.60 (t, 2H, C_7-CH_2), 2.15 (t, 2H, C_6-CH_2) ppm
5a	IR: υ = 3110 (Ar-H), 1634 (C=N), 1075 (C-O), 900 (N-O), 755 (C-Cl), 689 (C-S-C) cm^{-1}. ^1H NMR (DMSO-d_6): δ= 6.75-7.74 (m, 12H, Ar-H), 5.70 (s, 1H, CH_a), 4.60 (d, 1H, CH_b-O), 3.52 (d, 1H, CHc-S), 2.88 (t, 2H, C_7-CH_2), 2.28 (t, 2H, C_7-CH_2) ppm. Mass m/z : 503, 375, 363, 291, 290, 140, 111
5b	IR: υ = 3100 (Ar-H), 1638 (C=N), 1175 (C-F), 1080 (C-O), 902 (N-O), 752 (C-Cl), 690 (C-S-C) cm^{-1}. ^1H NMR (DMSO-d_6): δ= 6.60-7.80 (m, 12H, Ar-H), 5.68 (s, 1H, CH_a), 4.58 (d, 1H, CH_b-O), 3.49 (d, 1H, CH_c-S), 2.80 (t, 2H, C_7-CH_2), 2.24 (t, 2H, C_6-CH_2) ppm. Mass m/z : 487, 359, 347, 275, 274, 243, 140, 95
5c	IR: υ = 3108 (Ar-H), 1630 (C=N), 1078 (C-O), 898 (N-O), 750 (C-Cl), 685 (C-S-C) cm^{-1}. ^1H NMR (DMSO-d_6): δ= 6.48-7.80 (m, 12H, Ar-H), 5.62 (s, 1H, CH_a), 4.52 (d, 1H, CH_b-O), 3.85 (s, 3H, -OCH_3), 3.43 (d, 1H, CHc-S), 2.78 (t, 2H, C_7-CH_2), 2.19 (t, 2H, C_6-CH_2) ppm. Mass m/z: 499, 371, 359, 287, 286, 255, 140, 107
5d	IR: υ = 3102 (Ar-H), 1628 (C=N), 1071 (C-O), 895 (N-O), 751 (C-Cl), 680 (C-S-C) cm^{-1}. ^1H NMR (DMSO-d_6): δ= 6.25-7.45 (m, 13H, Ar-H), 5.60 (s, 1H, CH_a), 4.48 (d, 1H, CH_b-O), 3.48 (d, 1H, CHc-S), 2.74 (t, 2H, C_7-CH_2), 2.21 (t, 2H, C_6-CH_2) ppm. Mass m/z: 469, 341, 329, 257, 256, 225, 140, 77
5e	IR: υ = 3085 (Ar-H), 1638 (C=N), 1192 (C-F), 1078 (C-O), 910 (N-O), 750 (C-Cl), 690 (C-S-C) cm^{-1}. ^1H NMR (DMSO-d_6): δ= 5.74 (s, 1H, CH_a), 4.50 (d, 1H, CH_b-O), 3.54 (d, 1H, CH_c-S), 2.85 (t, 2H, C_7-CH_2), 2.29 (t, 2H, C_6-CH_2) ppm. Mass m/z: 487, 363, 359, 291, 290, 259, 124, 111
5f	IR: υ = 3078 (Ar-H), 1632 (C=N), 1185 (C-F), 1082 (C-O), 902 (N-O), 690 (C-S-C), 687 (C-S-C) cm^{-1}. ^1H NMR (DMSO-d_6): δ= 6.48-7.20 (m, 12H, Ar-H), 5.70 (s, 1H, CH_a), 4.48 (d, 1H, CH_b-O), 3.50 (d, 1H, CH_c-S), 2.74 (t, 2H, C_7-CH_2), 2.26 (t, 2H, C_6-CH_2) ppm. Mass m/z: 471, 347, 343, 275, 274, 124, 95
5g	IR: υ = 3082 (Ar-H), 1628 (C=N), 1190 (C-F), 1088 (C-O), 899 (N-O), 690 (C-S-C) cm^{-1}. ^1H NMR (DMSO-d_6): δ= 6.52-7.48 (m, 12H, Ar-H), 5.68 (s, 1H, CH_a), 4.56 (d, 1H, CH_b-O), 3.51 (d, 1H, CH_c-S), 2.70 (t, 2H, C_7-CH_2), 2.19 (t, 2H, C_6-CH_2) ppm. Mass m/z: 467, 343, 339, 286, 271, 255, 124, 107
5h	IR: υ = 3106 (Ar-H), 1633 (C=N), 1178 (C-F), 1082 (C-O), 907 (N-O), 688 (C-S-C) cm^{-1}. ^1H NMR (DMSO-d_6): δ= 6.64-7.75 (m, 13H, Ar-H), 5.63 (s, 1H, CH_a), 4.58 (d, 1H, CH_b-O), 3.48 (d, 1H, CH_c-S), 2.74 (t, 2H, C_7-CH_2), 2.28 (t, 2H, C_6-CH_2) ppm. Mass m/z: 453, 329, 325, 257, 256, 225, 124, 77

yl) is an ambivalent electrophile where the carbonyl carbon is hard and β-carbon is the soft centre. The conjugation of the double bond with the phenyl ring reduces the extent of its conjugation with the carbonyl group. Where as in case of hydroxylamine the nucleophilicity of N is increased due to adjacent oxygen atom, thus make it a harder nucleophile (α-effect). Hence the attack of NH_2 at carbonyl occurs first forming the isoxazole derivatives **5a-h** and not its alternate structure. The ^{1}H NMR spectrum of **5a** was in accordance with the proposed structure. The diagnostic methine products (O-CH-CH-S) attached to O and S appeared as clear doublet (J = 3.80 Hz) at around δ 4.60 and δ 3.52 respectively confirming the condensation reaction with hydroxylamine hydrochloride. Finally conclusive evidence has been gathered from the mass spectrum of all final compounds. The approach of generating the targeted systems has also been carried under thermal cyclisation conditions with a view to compare the effectiveness of microwave irradiation. Conventional heating gave product but in low yields compare to microwave irradiation. Physical and analytical data are presented in (Table 1) and spectral data are given in (Table 2).

Experimental Section

General Procedures. All the reactions were carried out in a domestic microwave oven (Kenstar, Model No. OM-26 EGO, Power 1200W). Melting points were determined in open capillaries. Reactions were monitored by thin layer chromatography using silica gel-G as adsorbent using ethyl acetate: benzene (1:9) as eluent. IR spectra (KBr pellets) were recorded on Perkin-Elmer 1800 (FTIR) Spectrometer. ^{1}H NMR spectra (DMSO-d_6) were taken a Bruker DRX spectrometer (300 MHz FT NMR) using TMS as internal standard and chemical shift are expressed in δ ppm. Mass spectra were taken on Jeol sx-102/PA-6000 (EI) spectrometer. Compounds **1a-d** were prepared according to literature reported.[22]

Synthesis of 4-Aryl-3,4,5,6-tetrahydrobenzo(h)quinazoline-2(1H) thiones (2a-d).

Conventional Method: A mixture of 2-arylidenetetralin-1-one **1a-d** (0.02 mol) and thiourea (0.02 mol) and KOH 2 g was taken in ethanol and refluxed for 4-6 hr. The reaction was monitored on TLC. After the completion of the reaction, it was cooled and the resulting solid was filtered, dried and recrystallized from ethanol to get compound **2a-d**.

Microwave Method: A mixture of 2-arylidenetetralin-1-one **1a-d** (0.02 mol) and thiourea (0.02 mol) in ethanolic KOH (1 g KOH in 25 mL ethanol) was irradiated under MWI for 5.30 min. with a time interval of 10 seconds. The volume of the reaction mixture was reduced to half and kept overnight. The solid thus separated as shining needles was filtered and washed with aqueous ethanol to give **2a-d**.

Synthesis of 5-Aryl-2,3,6,7-tetrahydro-3-oxo-5H-thiazolo-[2,3-b]benzo(h)quinazolines (3a-d).

Conventional Method: A mixture of thiones **2a-d** (0.01 mol), chloroacetic acid (0.01 mol), anhydrous sodium acetate (0.01mol), and acetic anhydride (2 mL) was taken in glacial acetic acid and refluxed for 3-5 hr. After cooling the reaction mixture, it was poured into ice cool water. The solid product was filtered, dried and recrystallized from acetic acid to get (**3a-d**).

Microwave Method: A mixture of thiones **2a-d** (0.01 mol), chloroacetic acid (0.01 mol), anhydrous sodium acetate (0.01mol), glacial acetic acid (15 mL) and acetic anhydride (2 mL) was irradiated under microwave irradiation for 2 min. using funnel as a loose top. The reaction mixture was cooled and poured into ice-cold water. The solid thus separated was filtered, washed with water and finally crystallized from glacial acetic acid to give **3a-d**.

Synthesis of 5-Aryl-2arylidine-2,3,6,7-tetrahydro-3-oxo-5H-thiazolo[2,3-b]benzo[h]quinazolines (4a-h).

Conventional Method: A mixture of **3a-d** (0.01 mol) and appropriate aromatic aldehydes (0.01 mol) was taken in glacial acetic acid. Anhydrous sodium acetate (0.02 mol) was added to it and refluxed for 3 hr. The reaction mixture was allowed to attain room temperature and treated with cold water. The solid thus separated was filtered, washed with water and recrystallized from glacial acetic acid to furnish compounds **4a-h**.

Microwave Method: Compounds **3a-d** (0.01 mol) was suspended in minimum quantity of ethanol. To this appropriate aromatic aldehydes (0.01 mol), anhydrous sodium acetate (0.02 mol) and glacial acetic acid (10 mL) were added and irradiated for the 1.50-2.50 min. The reaction mixture was cooled at room temperature and then poured into ice cold water. The separated solid was filtered, washed with water and crystallized from glacial acetic acid to give **4a-h**.

Synthesis of 7,11-Diphenyl5,6a,7,11,11a,13a-hexahydro-6H-benzo[h]isoxazolo[3',4',4,5][1,3]thiazolo[2,3-b]quinazolines (5a-h).

Conventional Method: A mixture of **4a-h** (0.01 mol) and hydroxylamine hydrochloride (0.012 mol) was taken in absolute ethanol. To it solution of sodium acetate (0.012 mol) in acetic acid (5 mL) was added slowly. It was refluxed for 10 h. The reaction mixture was kept for overnight and then solution was poured into water. The resulting solid was filtered, dried and recrystallized from acetic acid to get product **5a-h**.

Microwave Method: Solution of sodium acetate (0.012 mol) in acetic acid (5 mL) was added to a mixture of **4a-h** (0.01 mol) and hydroxylamine hydrochloride (0.012 mol) in absolute ethanol. The reaction mixture was irradiated for 6-8 min. under microwave and kept overnight, solution was poured into water. The solid thus obtained was crystallized from acetic acid to give **5a-h**.

Biological Screening. In view of antimicrobial activities of some quinazoline derivatives, it was of interest to incorporate this moiety into some heterocyclic molecules with the hope that the resulting compounds might exhibit enhanced activity compared to the parent quinazoline derivatives. The products and their parent substances were tested *in vitro* for their antibacterial activity against *Pseudomonas aeruginosa*, *Proteus mirabilis*, *Klebsiella pneumoniae*, *Bacillus subtilis*, and antifungal activity against *Aspergillus fumigatus*, *Candida*

Table 3. The antimicrobial activities of some synthesized compounds

Compd.	Antibacterial Activity (250 ppm)				Antifungal Activity (250 ppm)	
	Pseudomonas aeruginosa	*Proteus mirabilis*	*Klebsiella pneumoniae*	*Bacillus subtilis*	*Aspergillus fumigatus*	*Candida albicans*
3a	++	++	++	+	–	+
3b	–	+	–	+	++	–
3c	++	++	–	–	+	+
3d	–	–	++	++	+	–
5a	+++	+	–	+	++	+++
5b	–	–	+	–	–	++
5c	+++	++	+++	+++	++	–
5d	–	+++	+	++	–	+++
5e	+++	–	+++	–	+++	–
5f	++	+	–	++	++	+
5g	+++	+++	++	–	–	+++
5h	–	–	++	+++	++	+
Ciprofloxacin	+++	++	++	+++	–	–
Amphotericin B	–	–	–	–	+++	+++

–: No activity; +: moderate activity (inhibition zone: 5-10 mm); ++: strong activity (inhibition zone: 11-15 mm); +++: very strong activity (inhibition zone: 16-20 mm).

albicans, by the cup or well[23] method using DMF as a solvent at the concentration of 250 ppm. Commercial antibacterial Ciprofloxacin and antifungal Amphotericin B were also screened under similar conditions for comparison. The diameter of inhibition zones (mm) were measured and recorded. The results have been tabulated in the form of inhibition zones in (Table 3). The resulting compounds showed better activity against tested organisms. In general, the introduction of thiazolidinone and isoxazole heterocyclic system in the quinazoline nucleus results in the enhancement of the activity of the compounds.

Conclusion

In conclusion an efficient synthesis of quinazoline derivatives carrying potential pharmacophores like thiazolidinone and isoxazole have been prepared in an environmentally benign microwave protocol. The yields of the products formed under MWI were high in comparison to classical method (Table 1) and time required for completion of these reactions was also less in comparison to classical method. By visualizing the antimicrobial data (Table 3) it could be observed that most of the final compounds exhibited moderate to strong activities against all the tested organisms.

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