Synthesis and Biological study of some novel Quinazoline compounds

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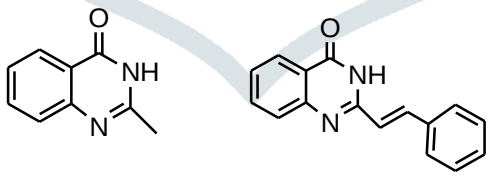
Abstract: The present paper describes, the synthesis of novel sulfur containing Quinazoline heterocyclic compound, through the addition of thiols to the various 2- styryl quinazoline molecules .The convenient, catalyst-free pathway was followed for this addition reaction. The newly synthesized compound was screened for their biological activities.

Key Words : Quinazoline, 2- styryl quinazoline , Thiols , Catalyst-free , Addition reaction, Biological activities.

I. Introduction:

Quinazoline- 4(3H) –one is one of the most promising privileged structural icon in medicinal Chemistry[18, 19] (Fig-1).Quinazoline 4(3H) one is a building block for various 2- styryl-4(3H) Quinazolione (Fig-1),which also gain great interest in the field of medicinal chemistry. It exhibits a wide spectrum of pharmaceutical activities such as antitumor[1, 2], anti-HIV[20], antimicrobial[15], antibacterial and antifungal[19], anti-inflammatory[4], anticonvulsant[9], sedative-hypnotic[8].Moreover, sulfur-containing organic compounds are also biological active substances[1]. They exhibits the wide range of pharmaceutical application such as antiviral, antibacterial, antiallergic, antimalarial and cytotoxic properties[7].

The biological properties of 2- styryl-4(3H) Quinazolione and its derivatives can be enhance by introducing sulfur on carbon –carbon double bond of 2- styryl-Quinazolione. The addition of thiol across carbon carbon double bond is performed under base catalyst, Lewis acid catalyst or proceeds through free radical pathway in presence of U.V light .But in the present work the convenient, catalyst-free pathway was followed for the synthesis of novel sulfur containing heterocyclic compound at room temperature and in aqueous medium.



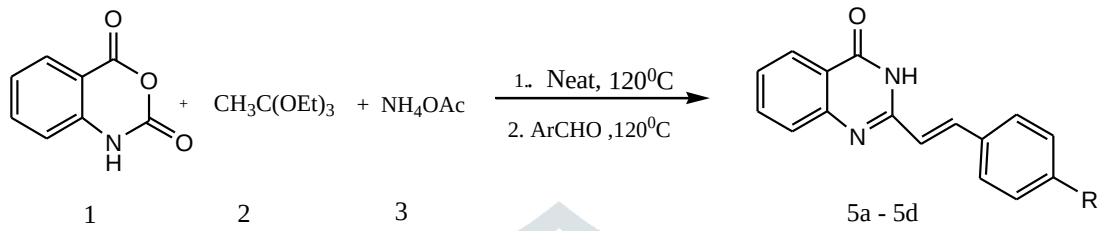
A B

Fig-1 Structure of A) 2- methyl quinazoline 4(3H)-one & B) 2- styryl quinazoline 4(3H)-one

II. Result and Discussion:-

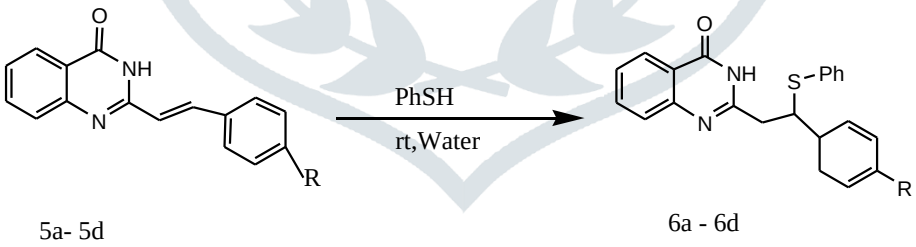
In the literature there were various synthetic strategies available for the synthesis of 2- styryl-4(3H) Quinazolione i) reaction of anthranilic acid with styryl carboxylic acid followed by amine/ammonia inseration[10], ii) Knoevenagel condensation of 2-methyl-Quinazolin-4(3H) one with aromatic aldehyde in presence of LDA[17] or in refluxing glacial acetic acid [13], iii) reaction between isatoic anhydride, triethyl orthoacetate, NH_4OAc followed by addition of aromatic aldehyde[5].

The first two methods are involve use of strong base as well as long reaction completion time,so the third pathway was followed in scheme I[st] ,as it was more convenient and efficient method over first two method as- one pot synthesis, required less time, solvent & catalyst free procedure. In this method the 1eq Isatoic anhydride ,1eq orthoester and 1.2eq NH_4OAc was treated to conventional heating at120°C for 4hrs followed by addition of aromatic aldehyde and further heated for 4 hrs. The reaction completion was checked by TLC .The yield of newly synthesis 2- styryl quinazolione compounds were found to be in range of 64-77% .The characterization of compounds was done by M.P,I.R and NMR.



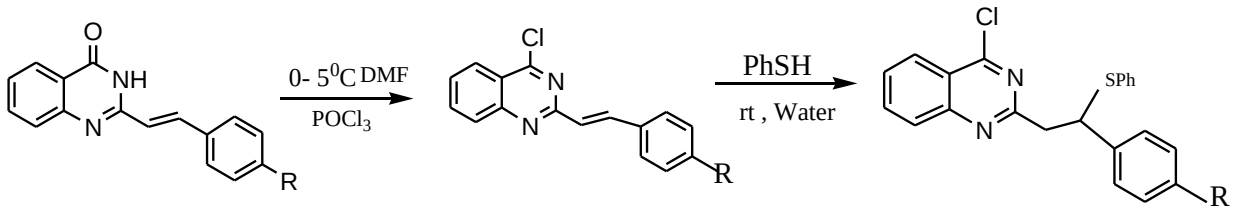
Scheme – 1 Synthesis of various 2-styryl 4(3H)-Quinazolione. R = -H, -Cl, -OMe, -N (CH_3)

In schemes II , various thiol derivatives (6a-6d) of Quinazolione were synthesized. There were different methods reported in literature which are either base[12] or Lewis acid catalyzed [14], U.V light catalyzed free radical reactions[6]. Initially the reaction was allowed to proceed through free radical pathway, but this pathway was reported to gave highly impure and low yield product. So however, a convient, catalyst free, aqueous medium addition pathway was followed[11]. In this method (5a-5d) – styryl quinazolione compounds was treated with thiophenol with vigorous stirring at room temperature, the progress of reaction was monitored by TLC ,time required to complete all reaction was reported 60-120 mins and yield was reported 60-74%. The characterization of compounds was done by M.P, TLC, IR &NMR.



Scheme -2 Synthesis of Thiol derivatives of 2-styryl 4(3H)-Quinazolione

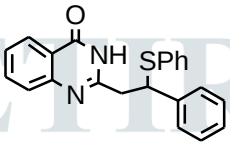
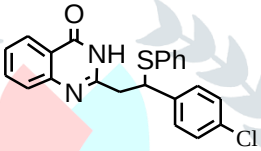
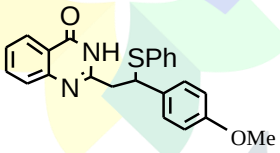
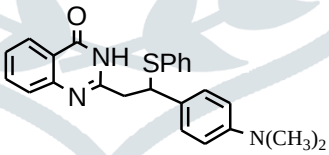
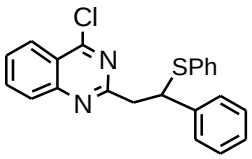
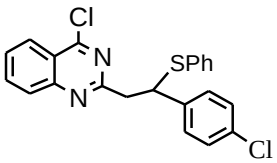
In the scheme III chloro derivatives of all (5a-5b) were synthesized .Chlorination reaction of 5a -5d was carried out in DMF at 0°C ,$POCl_3$ was added drop by drop over a period of 30min ,then allow to stir reaction mixture further ,until the TLC show complete disappearance of starting compound. The good yield was reported 83-95%.In the second step all the 2- styryl,4- chloro Quinazolione derivatives was subjected to thiol addition under the same condition reported in scheme II ,time required for all reaction was reported 60-120 mins and 65-75% yield was reported.The Characterization of compounds was done by M.P, TLC, IR and NMR

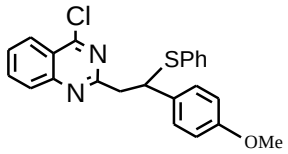
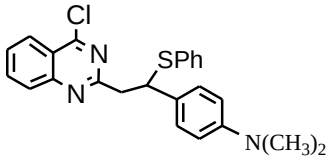


5a - 5d 7a - 7d 8a - 8d

Scheme -3 Synthesis of Thiol derivatives of 4- Chloro 2 –Styryl Quinazolione.

Table : 1 Addition of Thiol to 2- Styryl Quinazoline

Entry	2-styryl quinazoline	Thiol	Product	Yieid	M.P
1	5a	Thiophenol		65%	270^0
2	5b	Thiophenol		69%	310^0
3	5c	Thiophenol		60%	315^0
4	5d	Thiophenol		74%	275^0
5	7a	Thiophenol		75%	280^0
6	7b	Thiophenol		65%	285^0

7	7c	Thiophenol		66%	264^0
8	7d	Thiophenol		70%	295^0

III. Biological activity:-

All the newly synthesized thiol derivatives of Quinazolione compounds were screened for their antibacterial activity. For antibacterial studies microorganism employed were E.Coil, S.aureus, B.subtillis, P.aeruginosa. The study were assessed by minimum inhibitory concentration and the data was summarized in Table-2

Table : 2 Antibacterial activity of Compounds

Compounds	Zone of Inhibition (mm)			
	E. coli	S.aureus	B.subtilis	P.aeruginosa
6a	10	13	09	11
6b	12	08	13	08
6c	10	14	10	11
6d	15	09	11	13
8a	18	15	15	14
8b	17	16	14	17
8c	19	15	18	16
8d	20	16	13	18
Ciprofloxin	25	20	-	-

IV. Conclusion:

In conclusion, the present work reports simple, convenient, catalysts free, aqueous medium synthesis of novel sulphur introducing Quinazoline compound.The newly synthesized compound was evaluated for antibacterial activity. Among all tested compounds, 8c and 8d compound shows better biological activities.

V. Experimental Section :-

Representive experimental procedure for preparation of1, [2(phenyl), 2(phenylsulfanylethyl)] Quinazoline-4(3H)-one:-

A mixture of 5a (0.5gm,2mmol) ,Thiophenol (0.26gm,2mmol) and water 5ml was placed in a round bottom flask. The reaction mixture was magnetically stirred at room temperature. The progress of the reaction was monitored by TLC, until the starting compound had completely disappeared. Then the organic materials were extracted with $CHCl_3$, organic layer was washed with water .Dried over $MgSO_4$ and evaporation of the organic layer gave the crude product. Crude product was purified by column chromatography on silica gel n-Hexane/Ethyl acetate used as eluent to gave purified (6a)

as white solid. Yield: 65%, M.P:270oC. I.R: (KBr)ν_{max} : 3320(N-H)3132(C-H aromatic),1675(C=O),1585(C-S),1550(C=N),750(ArC-Hstreaching).^{1}HNMR(400MHzCDCl$_3$):δ=3.2(s.1H,D$_2$O exchangeable),3.02(d,2H, CH$_2$-CH-SPh), 3.5 (t,1H,-CH-CH$_2$), 7.53 (d,1H,J=7Hz,quinazolineC$_5$-H), 7.55 (d,1H,J=7Hz quinazolineC$_8$-H), 7.72-7.74 (m, 1H quinazolineC$_6$-H), 7.75-7.77 (m, 1H quinazolineC$_7$-H), 7.28-7.33 (m, 5H, phenyl-H), 7.40-7.45 (m, 5H, S-phenyl-H), .MS(APCl)m/z:357.2(M+H)$^+$,Elemental Analysis(found) :-C- 73.6%,H-5.03%,N-7.7%

Some selected spectral and analytical data:

1-[2-(4-methoxyphenyl), 2(phenylsulfanylethyl)] Quinazoline-4(3H)-one (6c):- Yield:-60 % M.P 315^{o}C. I.R (KBr)ν_{max}:3320(N-H),3132(C-H aromatic),1675(C=O),1586 (C-S),1550 (C=N) ,750 (Ar C-H stretching),1200(O-C).^{1}HNMR(400MHz,CDCl$_3$):δ=3.2(s.1H,D$_2$O exchangeable),3.02(d,2H, CH$_2$-CH-SPh), 3.5 (t,1H,-CH-CH$_2$), 7.53 (d,1H,J=7Hz,quinazolineC$_5$-H), 7.55 (d,1H,J=7Hz quinazolineC$_8$-H), 7.72-7.74 (m, 1H quinazolineC$_6$-H), 7.75-7.77 (m, 1H quinazolineC$_7$-H), 7.28-7.33 (m, 5H, phenylC-H), 7.40-7.45 (m, 5H, S-phenylC-H),7.9-7.95(d,2H,J=8.01Hz,C3,5-OMephenyl),7.2-7.25(d,2H,J=8Hz.C2,6-OMephenyl) ,3.32 (s,3H,OMe). MS(APCl)m/z:449.3(M+H)$^+$,Elemental Analysis(found) :-C- 72.01%,H-7.3%,N-6.27%

1-[2-(4- chloro phenyl), 2(phenylsulfanylethyl)] Quinazoline-4(3H)-one (6b):- Yield :-69 % M.P 310^{o}C. I.R (KBr)ν_{max} :3340(N-H)3132(C-H aromatic),1674(C=O),1586(C-S),1555(C=N) ,1080(Ar-Cl)751(Ar C-H stretching).^{1}HNMR(400MHz,CDCl$_3$):δ=3.3(s.1H,D$_2$O exchangeable),3.22(d,2H, CH$_2$-CH-SPh), 3.4 (t,1H,-CH-CH$_2$), 7.43 (d,1H,J=7Hz,quinazolineC$_5$-H), 7.45 (d,1H,J=7Hz quinazolineC$_8$-H), 7.74-7.745(m, 1H quinazolineC$_6$-H), 7.76-7.778(m, 1H quinazolineC$_7$-H), 7.30-7.35 (m, 5H, phenylC-H), 7.45-7.47 (m, 5H, S-phenylC-H) , 7.8-7.85(d,2H,J=8.01Hz,C3,5-Cl phenyl),7.23-7.25(d,2H,J=8Hz.C2,6-Cl phenyl). MS(APCl)m/z:438.15 (M+H)$^+$,Elemental Analysis(found) :-C- 68.6%,H-6.03%,N-6.7

1-[2-(phenyl), 2(phenylsulfanylethyl)] 4 chloro Quinazoline (8a):- Yield:-75 % M.P 280^{o}C. I.R (KBr)ν_{max} :3330(N-H)3132(C-H aromatic),1680(C=O),1586(C-S),1560(C=N) ,1085(Ar-Cl)755(Ar C-H stretching). N ^{1}HNMR(400MHz,CDCl$_3$):δ=3.22(s.1H,D$_2$O exchangeable),3.05(d,2H, CH$_2$-CH-SPh), 3.5 (t,1H,-CH-CH$_2$), 7.6 (d,1H,J=7Hz,quinazolineC$_5$-H), 7.7 (d,1H,J=7Hz quinazolineC$_8$-H), 7.7-7.72 (m, 1H quinazolineC$_6$-H), 7.8-7.82 (m, 1H quinazolineC$_7$-H), 7.38-7.4 (m, 5H, phenyl-H), 7.40-7.45 (m, 5H, S-phenyl-H) 7.2-7.25(m,5H,C5 -phenyl),,MS(APCl)m/z:422.16(M+H)$^+$,Elemental Analysis(found) :-C- 70.6%,H-6.53%,N-6.7

1-[2-(4-chlorophenyl), 2(phenylsulfanylethyl)] 4 chloro Quinazoline (8b):- Yield :-65 % M.P 285^{o}C. I.R (KBr)ν_{max} :3323(N-H)3132(C-H aromatic),1678(C=O),1578(C-S),1560(C=N) ,1080(Ar-Cl),750(Ar C-H stretching).^{1}HNMR(400MHz,CDCl$_3$):δ=3.1(s.1H,D$_2$O exchangeable),3.12(d,2H, CH$_2$-CH-SPh), 3.5 (t,1H,-CH-CH$_2$), 7.52 (d,1H,J=7Hz,quinazolineC$_5$-H), 7.56 (d,1H,J=7Hz quinazolineC$_8$-H), 7.72-7.76 (m, 1H quinazolineC$_6$-H), 7.75-7.8 (m, 1H quinazolineC$_7$-H), 7.28-7.33 (m, 5H, phenylC-H), 7.40-7.45 (m, 5H, S-phenylC-H),7.87-7.9(d,2H,J=8.01Hz,C3,5-Clphenyl),7.28-7.3(d,2H,J=8Hz.C2,6-Clphenyl) MS (APCl)m/z :456.2(M+H)$^+$, Elemental Analysis(found) :-C- 65.6%,H-5.63%,N-6.2%

1-[2-(4-methoxyphenyl), 2(phenylsulfanylethyl)] 4-chloro Quinazoline (8c):- Yield:-66 % M.P264^{o}C.I.R (KBr)ν_{max} :3330(N-H)3132(C-H aromatic),1685(C=O),1586(C-S),1565(C=N) ,1229(C-O),750 (Ar C-H stretching).^{1}HNMR(400MHz,CDCl$_3$):δ=3.32(s.1H,D$_2$O exchangeable),3.1(d,2H, CH$_2$-CH-SPh), 3.4 (t,1H,-CH-CH$_2$), 7.54 (d,1H,J=7Hz,quinazolineC$_5$-H), 7.6(d,1H,J=7Hz quinazolineC$_8$-H), 7.7-7.74 (m, 1H quinazolineC$_6$-H), 7.8-7.82 (m, 1H quinazolineC$_7$-H), 7.22-7.23 (m, 5H, phenyl-H), 7.5-7.55 (m, 5H, S-phenyl-H),7.9-7.96(d,2H,J=8.01Hz,C3,5-OMephenyl),7.25-7.27(d,2H,J=8Hz.C2,6-OMe-phenyl), 3.35 (s,3H,OMe).MS(APCl)m/z:452.15(M+H)$^+$,Elemental Analysis(found):-C-68.8%,H-6.43%

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