Synthesis and antibacterial activity of 2-phenyl-5-aryl-4, 5, 6, 7, 8, 9- hexahydro-1,2.4-triazolo[1,5-A]quinazolines

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Síntesis y actividad antibacteriana de 2-fenil-5-aril-4, 5, 6, 7, 8, 9 - hexahidro-1,2.4-triazolo [1,5-a] quinazolinas

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Recibido: 17 de marzo de 2013; aceptado: 11 de abril de 2013

RESUMEN

Se ha desarrollado un método para la síntesis de 2-fenil-5-aril-4, 5, 6, 7, 8, 9 - hexahydrotriazolo [1,5-*a*] quinazolinas. El 3-amino-5-fenil-1,2,4-triazol forma bases de Schiff con aldehídos aromáticos que en el tratamiento con ciclohexanona en presencia de ácido acético glacial y cloruro de cinc anhidro se cicla para producir los compuestos del título. Las estructuras de los compuestos sintetizados fueron determinadas mediante técnicas espectroscópicas (FTIR y ^{1}H-RMN) y análisis elemental. La actividad antibacteriana de los compuestos también se examinó frente a cuatro cepas bacterianas diferentes por el método de disco de placa de agar.

Palabras clave: Reacción Doebner-Miller, triazoles, bases de Schiff, espectros de RMN, espectros de masas.

SUMMARY

A method for the synthesis of 2-phenyl-5-aryl-4, 5, 6, 7, 8, 9- hexahydrotriazolo[1,5-*a*] quinazolines was developed. 3-Amino-5-phenyl-1,2,4-triazole formed Schiff's bases with aromatic aldehydes which on treatment with cyclohexanone in the presence of glacial acetic acid and anhydrous zinc chloride cyclized to produce title compounds. The structures of synthesized compounds were elucidated by spectroscopic techniques (FTIR and ^{1}H-NMR) and elemental analysis. The compounds were also screened for their antibacterial activities against four different bacterial strains by agar plate disc method.

Key words: Doebner-Miller Reaction, Triazoles, Schiff's bases, NMR Spectra, Mass Spectra.

RESUM

S'ha desenvolupat un mètode per a la síntesi de 2-fenil-5-aril-4, 5, 6, 7, 8, 9 - hexahydrotriazolo [1,5-*a*] quinazolines. El 3-amino-5-fenil-1,2,4-triazole forma bases de Schiff amb aldehids aromàtics, els quals al ser tractats amb ciclohexanona en presència d'àcid acètic glacial i clorur de zinc anhidre es cicla per produir els compostos del títol. Les estructures dels compostos sintetitzats van ser determinades mitjançant tècniques espectroscòpiques (FTIR i 1H-RMN) i anàlisi elemental. L'activitat antibacteriana dels compostos també es va examinar contra quatre soques bacterianes diferents pel mètode de disc de placa d'agar.

Paraules clau: Reacció Doebner-Miller, triazols, bases de Schiff, espectres de RMN, espectres de masses.

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INTRODUCTION

Triazole derivatives show a variety of pharmacological, fungicidal, herbicidal and insecticidal activities [1-7]. 1,2,4-Triazoles belong to a new class of antimicrobial agents, fluconazole **(I)** and itraconazole are being used as antimicrobial drugs [8,9]. It has also been reported that biheterocyclic compounds containing 1,2,4-triazole ring are good antimicrobial agents[10-13], The generally known systems fused to triazoles are pyridines, pyridazines, quinazolines, pyrazines and triazines[14-17].

Quinazolines and condensed quinazolines on the other hand also possess diverse pharmacological activities and they are used as potent tyrosine kinase inhibitors [18, 19]. Triazoloquinazolines constitute an important class of pharmaceutically important compounds[20-22]. More recently reported 1,2,4-triazoloquinazolines **(II)** exhibited antihistaminic activity[23, 24].A 1,2,3-triazolo[1,5-*a*]quinazoline was first reported 36 years ago by Tennant; anthranilic acid was used as the starting material for this synthesis. Anthranilic acid was converted into 2-azidobenzoic acid by diazotisation followed by reaction with the isoxazole acetonitrile to give the final product[25].

5,6,7,8-Tetrahydro-4*H*-spiro{[1,2,3]triazolo[5,1-*b*]quinazoline-9,1'-cyclohexane}-3-carboxamide **(III)** was prepared by the reaction of 4-amino-5-carboxamido-1,2,3-triazole with cyclohexanone in dry ethanol for three hours. The yield of the reaction was improved by carrying out this reaction under microwave irradiation for 20 minutes at 120°C using methanol solvent[26]. A condensation of 3-substituted 5-amino-1,2,4-triazoles with 2-cyclohexylidenecyclohexanone in DMF resulted in the synthesis of 2′-substituted 5′,6′,7′,8′-tetrahydro-4′*H*-spiro[cyclohexane-1,9′-[1,2,4] triazolo[5,1-*b*]quinazolines] which were hydrogented by using sodium borohydride in ethanol to give 2′-substituted *cis*-4a',5′,6′,7′,8′,8a'-hexahydro-4′*H*-spiro[cyclohexane-1,9′-[1,2,4]triazolo[5,1-*b*]quinazolines] [27].

A general method for the synthesis of triazoloquinazolines involves the reaction of hydrazinoquinazolines with aliphatic carboxylic acid or their esters[28-31]. 3-Phenyl-s-triazolo[4,3-*c*]quinazoline was prepared by heating 4-(3-phenyltetrazolyl)quinazoline[32].

The mechanism for the synthesis of benzopyrimidine heterocycle has been studied. The heterocyclization reaction of 3-amino-1,2,4-triazole with arylidene derivatives of dimedone resulted in the synthesis of 9-aryl-6,6-dimethyl-5,6,7,9-tetrahydro-1,2,4-triazolo[5,1-*b*]quinazolin-8-ones[33].

In view of the above findings, we have synthesized some novel derivatives of triazolo[1,5-*a*]quinazoline (2a-g) (**Scheme 1**) via the Schiff's bases from 3-amino-5-phenyl-1,2,4-triazole and are reported in this paper. The synthesized compounds were also tested for their antibacterial activities.

MATERIALS AND METHODS

All the chemicals used in this synthesis were of analytical grade and were mostly used without further purification. The starting material 3-amino-5-phenyl-1,2,4-triazole was obtained commercially. Melting points were determined on a Gallenkamp melting point apparatus. Infrared spectrometer Shimadzu-408 was used for measuring the spectra in KBr disks. Proton magnetic resonance (PMR) spectra were taken on a Brucher 300 and 500 MHz spectrometer. Elemental analysis were determined on a Perkin-Elmer model 240. Mass spectra were recorded on a Finnigan MAT 112.

Synthesis of Schiff base (1a-g)[34].

3-(Benzylidene)-5-phenyl-1,2,4-triazole (1a)

General Method: Equimolar quantities of 3-amino-5-phenyl-1,2,4-triazole (1.60 g; 0.01 mole) benzaldehyde (1.06g; 0.01 mole) and aluminium chloride (0.1g) were dissolved in absolute ethanol (10mL). It was refluxed for two hours on a water bath with occasional shaking. On cooling at room temperature white precipitates obtained were filtered, dried and recrystallized from ethanol
m.p. 190°C; Yield: 70 %
Compounds **1b-1g** were prepared from 3-amino-5-phenyl-1,2,4-triazole and the corresponding aldehydes by the above general method.

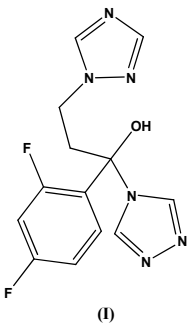
3-(*o*-nitrobenzylidene)-5-phenyl-1,2,4-triazole (1b): m.p. 145°C ; Yield: 72%

3-(*o*-methoxybenzylidene)-5-phenyl-1,2,4-triazole (1c): m.p. 170°C ; Yield: 68%

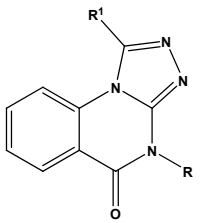
3-(*o*-bromobenzylidene)-5-phenyl-1,2,4-triazole (1d): m.p. 160°C ; Yield: 60%

3-(*o*-chlorobenzylidene)-5-phenyl-1,2,4-triazole (1e): m.p. 155°C ; Yield: 73%

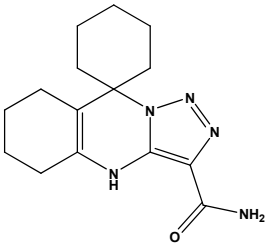
3-(2,4-dichlorobenzylidene)-5-phenyl-1,2,4-triazole (1f): m.p. 160°C ; Yield: 76%



(I)



R: alkyl, aryl, aralkyl
R1: alkyl, aryl
(II)



(III)

3-(*o*-hydroxybenzylidene)-5-phenyl-1,2,4-triazole (1g):
m.p. 130°C ; Yield: 76%

Synthesis of 2-phenyl-5-aryl-4, 5, 6, 7, 8, 9- hexahydro-1,2,4-triazolo[1,5-*a*]quinazolines (2a-g).

4, 5, 6, 7, 8, 9- Hexahydro-2,5-diphenyl-1,2,4-triazolo[1,5-a]quinazoline (2a)

General Method: A mixture of schiff base [1a], (2.48g, 0.01 mole), cyclohexanone (0.98g, 0.01 mole) and anhydrous zinc chloride (1.0g) was refluxed in glacial acetic acid (10mL) for six hours. On cooling the reaction mixture was poured over crushed ice with continuous stirring and allowed to stand for thirty minutes. The solid product which separated out was filtered, washed with excess of water, dried and recrystallized from ethanol to give the desired cyclic product.
m.p. 190°C; Yield: 68%
IR (KBr) cm^{-1}: 3300, 3050 (NH), 2850, 1700, 1650 (C=N), 1590 (C=C), 650.
^{1}H-NMR (DMSO d_6) δ: 1.80 (8H, m, 4×CH_2), 2.30 (1H, s, H-5), 7.30-9.30 (10H, m, Ar-H), 9.32 (1H, s, NH).
CHN: $C_{21}H_{20}N_4$, Calculated: C: 77.30, H: 5.52, N: 17.28 %. Found: C:77.34, H: 5.50, N: 17.15 %.

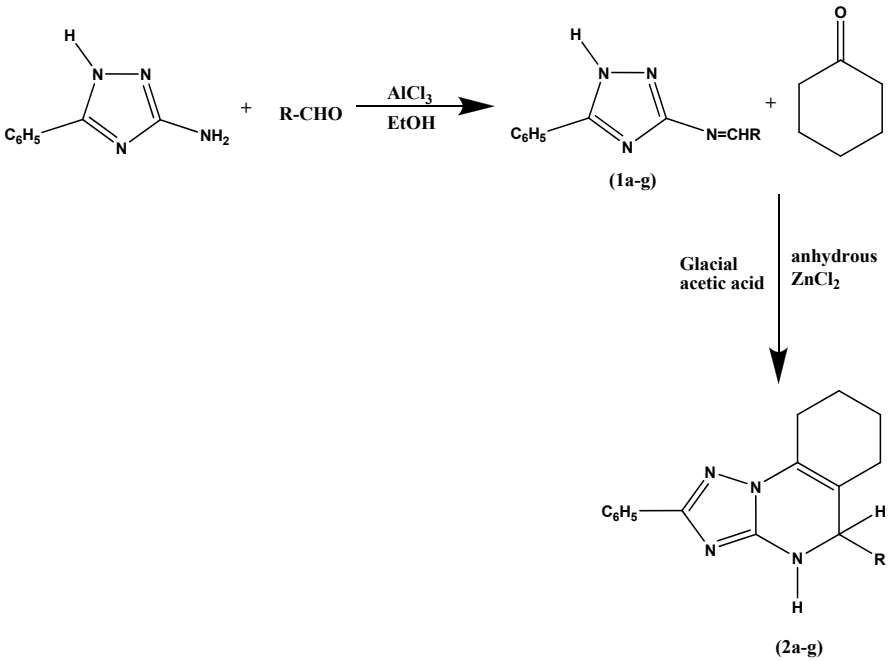
4, 5, 6, 7, 8, 9- Hexahydro-5-*o*-nitrophenyl-2-phenyl-1,2,4-triazolo[1,5-*a*]quinazoline (2b):
m.p. 130°C; Yield: 79%
IR (KBr) cm^{-1}: 3150 (NH), 1702, 1590 (C=C),1520, 1340 (NO_2).
^{1}H-NMR (DMSO d_6) δ: 1.68 (8H, m, 4×CH_2), 2.30 (1H, s, H-5), 6.83-8.42 (10H, m, Ar-H), 9.50 (1H, s, NH).
CHN: $C_{21}H_{19}N_5O_2$, Calculated: C: 67.92, H: 4.58, N: 18.87 %. Found: C:67.96, H: 4.55, N: 18.85 %

6, 7, 8, 9- Tetrahydro-5-*o*-methoxyphenyl-2-phenyl-1,2,4-triazolo[1,5-*a*]quinazoline (2c):
m.p. 180°C; Yield: 68%
IR (KBr) cm^{-1}: 2835 (OCH_3), 1720, 1635, 1550 (C=N), 1410.
^{1}H-NMR ($CHCl_3$)δ: 1.80 (8H, m, 4×CH_2), 2.55 (3H, m, OCH_3), 7.30-7.85 (10H, m, Ar-H).
CHN: $C_{22}H_{20}N_4O$, Calculated: C: 74.16, H: 5.62, N: 15.73 %. Found: C:74.13, H: 5.60, N: 15.75 %
MS: m/z (%) = $C_{22}H_{20}N_4O$ [M^+]: 366

4, 5, 6, 7, 8, 9- Hexahydro-5-*o*-bromophenyl-2-phenyl-1,2,4-triazolo[1,5-*a*]quinazoline (2d):
m.p. 170°C; Yield: 65%
IR (KBr) cm^{-1}: 3200, 3100 (NH), 1580 (C=C), 1210, 1140.
^{1}H-NMR (DMSO d_6) δ: 1.72 (8H, m, 4×CH_2), 2.22 (1H, s, H-5), 6.83-8.00 (10H, m, Ar-H), 9.30 (1H, s, NH).
CHN: $C_{21}H_{19}N_4Br$, Calculated: C: 62.22, H: 4.20, N: 13.83, Br: 19.75 %. Found: C:62.25, H: 4.23, N: 13.80, Br: 19.75 %.

4, 5, 6, 7, 8, 9- Hexahydro-5-*o*-chlorophenyl-2-phenyl-1,2,4-triazolo[1,5-*a*]quinazoline (2e):
m.p. 152°C; Yield: 80%
IR (KBr) cm^{-1}: 3100, 1670 (C=N), 1600 (C=C), 1470, 1260.
^{1}H-NMR ($CHCl_3$) δ: 1.84 (8H, m, 4×CH_2), 2.43 (1H, s, H-5), 6.43-7.76 (10H, m, Ar-H), 9.45 (1H, s, NH).
CHN: $C_{21}H_{19}N_4Cl$, Calculated: C: 69.90, H: 4.72, N: 15.53, Cl: 9.85 %. Found: C:69.94, H: 4.69, N: 15.50, Cl: 9.85 %.

4, 5, 6, 7, 8, 9- Hexahydro-5-(2,4-dichlorophenyl)-2-phenyl-1,2,4-triazolo[1,5-*a*]quinazoline (2f):
m.p. 170°C; Yield: 79%
IR (KBr) cm^{-1}: 3250, 3100, 2990, 1580 (C=C), 1455, 1325.
^{1}H-NMR (DMSO d_6) δ: 1.72 (8H, m, 4×CH_2), 2.18 (1H, s, H-5), 6.80-7.92 (10H, m, Ar-H), 9.28 (1H, s, NH).



R= C_6H_5, o-$NO_2C_6H_4$, o-BrC_6H_4, o-$OCH_3C_6H_4$, o-ClC_6H_4, 2,4-$Cl_2C_6H_3$, o-OHC_6H_4

(Scheme 1)

CHN: $C_{21}H_{18}N_4Cl_2$, Calculated: C: 63.80, H: 4.05, N: 14.18, Cl: 17.97 %. Found: C:63.83, H: 4.02, N: 14.20, Cl: 17.97 %.

4, 5, 6, 7, 8, 9- Hexahydro-5-*o*-hydroxyphenyl-2-phenyl-1,2,4-triazolo[1,5-*a*]quinazoline (2g):
m.p. 190°C; Yield: 78%
IR (KBr) cm^{-1}: 3120, 2840, 1690 (OH), 1595 (C=C), 645.
^{1}H-NMR (DMSO d_6) δ: 1.5-3.50 (8H, m, 4×CH_2), 4.22 (1H, s, OH), 4.29 (1H, s, H-5), 6.80-8.40 (10H, m, Ar-H), 8.37 (1H, s, NH).
CHN: $C_{21}H_{20}N_4O$, Calculated: C: 73.86, H: 5.62, N: 16.38 %. Found: C:73.40, H: 6.02, N: 16.18 %.
MS: m/z (%) = $C_{21}H_{20}N_4O$ [M^+]: 344

RESULTS AND DISCUSSION

3-Amino-5-phenyl-1,2,4-triazole was used as a starting material for the preparation of 2-phenyl-5-aryl-4, 5, 6, 7, 8, 9- hexahydro-1,2,4-triazolo [1,5-*a*] quinazolines **(2a-g) (Scheme 1)**. As triazole derivatives and quinazolines have been reported to possess diverse pharmacological activities, so this 1,2,4-triazolo[1,5-*a*]quinazoline system was prepared keeping in view the biological importance of both the ring systems.
3-Amino-5-phenyl-1,2,4-triazole condensed with aromatic aldehydes in absolute ethanol by using $AlCl_3$ as catalyst to give the respective Schiff bases **(1a-g)** which have already been reported previously[34]. These Schiff bases with cyclohexanone in the presence of zin chloride and glacial acetic acid cyclized to produce the corresponding 2-phenyl-5-aryl-4, 5, 6, 7, 8, 9- hexahydro-1,2,4-triazolo[1,5-*a*]quinazolines **(2a-g)** (**Scheme-1**). Glacial acetic acid has proved to be a good reaction medium, as it acts both as a solvent and as an acid co-catalyst together with anhydrous zinc chloride for this cyclization reaction with cyclohexanone. Using diverse benzaldehydes, corresponding products **2a-2g** were obtained in good to excellent yields (65-80 %).
The reaction was monitored through the melting points, TLC and IR data of the products. Normally in this type of condensation/cyclization reactions (Doebner-Miller Reaction[35]), the intermediate dihydro product often undergoes dehydration to furnish a fully aromatic ring. Here it seems that except **2c** the other products were not oxidized under these reaction conditions. The formation of hexahydro-1,2,4-triazolo[1,5-*a*]quinazolines **(2a-2b, 2d-2g)** was confirmed by IR, ^{1}H-NMR, MS and satisfactory elemental analysis data.
The IR data of **(2a)** showed a strong absorption at 3100 cm^{-1} indicated the presence of NH group confirmed the synthesis of non-aromatized product. Similarly the other characteristic absorptions were observed due to the presence of different substituents. In **(2b)** the presence of NO_2 group is indicated by the absorption bands at 1520 and 1340 cm^{-1}. In **(2c)** and **(2g)** the presence of $OCH_3$and OH were indicated by the strong absorptions at 2835 and 1690 cm^{-1} respectively. In **(2c)** the absence of absorption due to NH above 3100 cm^{-1} confirmed the formation of tetrahydro-1,2,4-triazolo[1,5-a]quinazoline.
The ^{1}H-NMR data of compounds (**2b**-**g**) showed a singlet at δ 2.30 due to aliphatic proton (H-5). A multiplet centred at δ 2.50 due to aliphatic protons (4×CH_2) and NH proton appeared at δ 9.32 as a singlet. A multiplet centred at δ 8.30 is assigned to aromatic protons. The PMR data of compound **(2b)** shows signals for aromatic protons as multiplet centred at δ 7.57. Another multiplet at δ 2.65 is observed due to three methoxy protons. A singlet at δ 2.12 due to an aliphatic proton (H-5) and a multiplet centred at δ 1.80 due to CH_2 (aliphatic) protons. Another singlet displayed at δ 9.30 is due to NH proton. The PMR data of **(2g)** shows characteristic signals of aromatic protons centred at δ 7.50 as multiplets. At δ 4.22 a singlet is observed for OH. Another multiplet showing signals at δ 1.5-3.50 are due to CH_2 protons of quinazoline.
Satisfactory elemental analysis and mass spectral data correspond to a particular molecular ion peak of all the cyclized products confirmed the formation of triazolo [1,5-a] quinazoline (2a-g). Mass spectra of **(2c)** showed molecular ion peak m/z 356 according to molecular formula $C_{22}H_{20}N_4O$. Mass spectrum of **(2g)** revealed a molecular ion peak at m/z 344 as expected, a hexahydro product, having molecular formula $C_{21}H_{20}N_4O$. The mass fragmentation pattern **(Scheme 2)** showed a peak at m/z 251 corresponds to the loss of C_6H_4OH (m/z 93) from the parent molecular ion peak. After this a base peak is obtained at m/z 185 due to loss of C_4H_4 (m/z 52) and CH_2 (m/z 14). Further loss of C_2H_4 (m/z 26), N_2 (m/z 28) and 2CN (m/z 26 × 2=52) simultaneously, created a shorter fragment, corresponding to C_6H_5 (m/z 77).

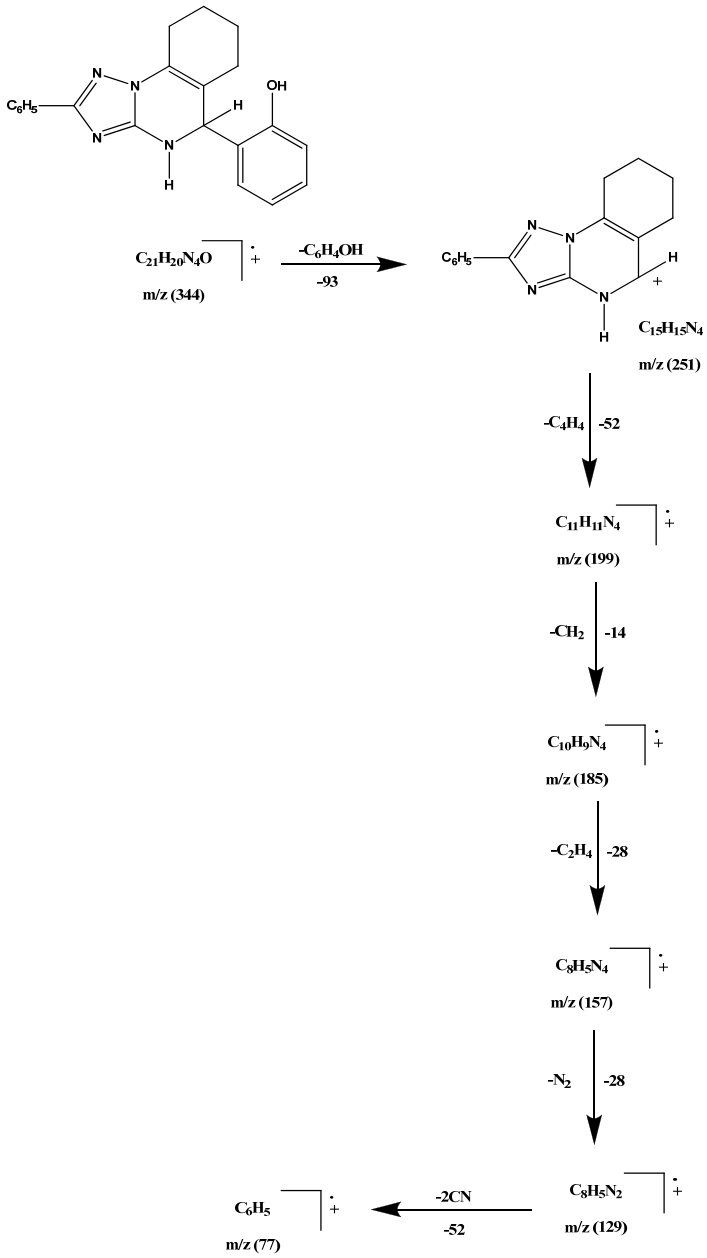
Antibacterial activity

Antibacterial activity of hexahydro-1,2,4-triazolo[1,5-*a*] quinazolines (**2a-g**) was tested by Agar plate disc diffusion method[36] against six different bacterial strains; *Staphylococcus aureus* (gram +ve), *Pseudomonas* (gram –ve), *Escherichia coli* (gram –ve) and *Klebsiella* (gram –ve). The filter paper disc (6.00 mm in diameter) was soaked with the solution of 50 mg of compound in 1 mL of chloroform was placed in the centre of plate. The plates were incubated with the growing cultures of bacterial strains.
The four different types of bacterial cultures were inoculated and were further incubated at 37°C for 24-48 hours. Vibramycin and Cefizox were used as standards. The test organism *S.aureus* and *E. coli* showed an inhibition zone of (30 mm) for Vibramycin while *Pseudomonas* showed resistance. *Klebsiella* showed an inhibition zone of (10 mm) for Vibramycin and (20 mm) for Cefizox, while in case of Cefizox no antibacterial activity was observed in *S. aureus* and *E. coli* but *klebsiella* showed an inhibition zone of 20 mm.
In case of antibacterial activity of synthesized compounds (**2a-g**), only two compounds **2c** and **2g** showed moderate activity against *S.aureus*, *Klebsiella*, *Pseudomonas* and *E. coli*. The results of antibacterial activity are given in **Table-1.**

Table 1. Antibacterial Activity of 1,2,4-triazolo [1,5-a] quinazolines 2a-2g

Compound No.	*S.aureus*	*Klebsiella*	*Pseudomonas*	*E. coli*
2a	-	-	-	-
2b	-	-	-	-
2c	-	20	-	17
2d	-	-	-	-
2e	-	-	-	-
2f	-	-	-	-
2g	25	-	20	12
VIB	30	10	-	30
CEF	-	20	-	-

VIB: Vibramycin, CEF: Cefizox



Scheme 2: Mass Fragmentation Pattern of 2g

CONCLUSIONS

The method used for the synthesis of 1,2,4-triazolo[1,5-*a*] quinazolines is a mild and efficient one as it gives better yields (65-80%). Schiff's bases being the reactive intermediate, their preformation or *in situ* formation both gave satisfactory results. The synthesized compounds showed moderate activity against some bacterial strains.

ACKNOWLEDGEMENTS

Areesha Nazeer likes to thank HEC, Govt. of Pakistan for an Indigenous and an IRISP scholarship.

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