

Synthesis and Antimicrobial Activities of a New Class of 6-Arylbenzimidazo[1,2-c]quinazolines

Rondla Rohini,^a Kanne Shanker,^a P. Muralidhar Reddy^b and Vadde Ravinder^{*,a}

^aDepartment of Chemistry, Kakatiya University, Warangal-506 009, A.P., India

^bDepartment of Chemistry, National Dong Hwa University, Hualien, Taiwan

Uma série de compostos 6-arylbenzimidazo[1,2-c]quinazolina (**11-20**) foram sintetizados pela condensação do 2-(*o*-aminofenil)benzimidazol com diferentes arilaldeídos seguida pela ciclização oxidativa dos 2-*o*-arilidenoaminofenilbenzimidazol (**1-10**). Todos os produtos foram caracterizados por espectroscopia no infravermelho (IR), ressonância magnética nuclear de prótons e de carbono, (RMN ¹H e RNN ¹³C), de massas (MS) e análise elementar. A atividade antimicrobiana de todos os 6-arylbenzimidazo[1,2-c]quinazolina foi testada com três linhagens de bactérias Gram-positivas (*S. aureus*, *B. subtilis* e *S. pyogenes*), três Gram-negativas (*S. typhimurium*, *E. coli* e *K. pneumonia*) e de três linhagens de fungos (*A. niger*, *C. albicans* e *T. viridae*). Dos compostos testados, o **13**, o **19** e o **20** mostraram-se ser os mais potentes inibidores contra os organismos testados.

A series of 6-arylbenzimidazo[1,2-c]quinazoline compounds (**11-20**) were synthesised by the condensation of 2-(*o*-aminophenyl)benzimidazole with different arylaldehydes, followed by oxidative cyclisation of the resulting 2-*o*-arylideneaminophenylbenzimidazoles (**1-10**). All the products were characterized via IR, ¹H NMR, ¹³C NMR, MS and elemental analysis. The antimicrobial activities of all 6-arylbenzimidazo [1,2-c]quinazolines against three Gram-positive (*S. aureus*, *B. subtilis*, *S. pyogenes*), three Gram-negative (*S. typhimurium*, *E. coli*, *K. pneumonia*) bacteria and three fungal strains (*A. niger*, *C. albicans*, *T. viridae*) were evaluated. Among the compounds tested **13**, **19** and **20** showed most potent inhibitory action against test organisms.

Keywords: 6-Arylbenzimidazo[1,2-c]quinazolines, synthesis, antibacterial activity, antifungal activity

Introduction

Heterocycles have a central position in medicinal as well as in organic chemistry¹⁻³ and considerable attention has been focused on their syntheses. Nitrogen heterocycles in particular exhibit diverse biological and pharmacological activities⁴⁻⁶ due in part to the similarities with many natural and synthetic molecules with known biological activity.⁷ Moreover, benzimidazoles and quinazolines are of the most extensively studied classes of heterocyclic compounds, and have received much attention from synthetic organic as well as medicinal chemists, because of the diverse range of their biological activities^{8,9} and their applications in several areas as materials in electronics, in electrochemistry as anticorrosive agents, as polymers or optical materials and fluorescent tags in DNA sequencing.¹⁰⁻¹² In general,

quinazoline compounds have been well-recognized for their pharmacological properties, such as anti-inflammatory,^{13,14} antihypertensive,¹⁵ anti-HIV,¹⁶ bronco-dilatory,¹⁷ anti-allergic,¹⁸ anti-cancer,¹⁹⁻²¹ anticonvulsant,^{22,23} antihelmintic,²⁴ analgesic,²⁵ antimalarial²⁶ and antimicrobial²⁷ activities. Literature survey reveals that, benzimidazo [1,2-c]quinazoline derivatives also show various biological activities,^{23,28-30} such as anticancer, antiviral, antimicrobial, anti-inflammatory and anticonvulsants. However, search is continuously on to identify a more potent lead molecule as these molecules are developing resistance over a period. Based on the importance of these molecules, our attention was attracted towards synthesis of novel quinazoline derivatives in order to find more potent biologically active molecules. Hence, we report here the synthesis and characterization of new 6-arylbenzimidazo[1,2-c]quinazoline compounds (**11-20**). In addition, the antimicrobial activities of all synthesized quinazolines against different bacteria and

*e-mail: ravichemku@rediffmail.com

fungi were evaluated. Among the compounds tested some of quinazolines were found to be superior in inhibiting all the bacterial and fungal strains.

Results and Discussion

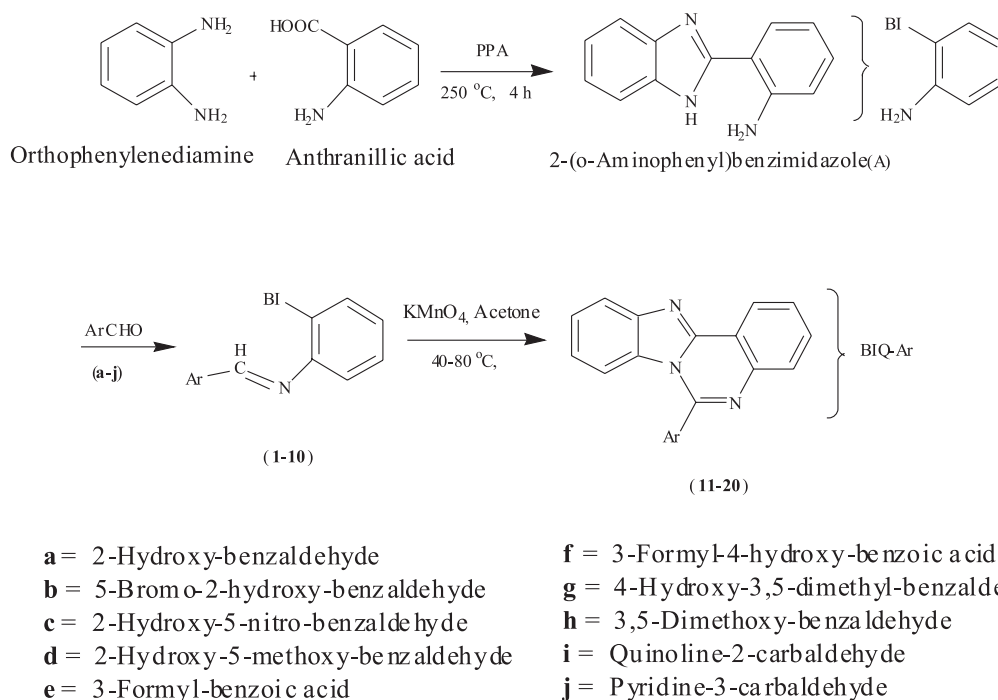
Chemistry

The condensation of *o*-phenylenediamine with anthranilic acid was carried out in presence of polyphosphoric acid at 250 °C for 4 h to obtain the known 2-(*o*-aminophenyl) benzimidazole (**A**) (mp 214 °C).³¹ The target compounds were prepared by using the reaction sequence in Scheme 1. Initially, we synthesised ten new 2-*o*-arylideneaminophenylbenzimidazoles (**1-10**) via the condensation between 2-(*o*-aminophenyl) benzimidazole(**A**) and various arylaldehydes. At last, we prepared 6-arylbenzimidazo [1,2-*c*] quinazolines (**11-20**) through oxidative cyclisation³² of 2-*o*-arylideneaminophenylbenzimidazoles (**1-10**).

IR spectra of compound **A** showed absorption band at 3350 cm⁻¹ assigned to aminophenyl ring and in the case of compounds **A** and **1-10** two absorption bands in the region 3150-3300 cm⁻¹ and 1420 cm⁻¹ were assigned to –NH stretching and bending vibrations of imidazolyl ring, respectively.^{33,34} The absence of aminophenyl ring absorption at 3350 cm⁻¹ and appearance of a strong intensity band in the IR spectra of compounds (**1-10**) in the range of 1610-1650 cm⁻¹

attributable to νC=N provides a strong evidence for the condensation and also confirms the formation of the azomethines **1-10**.³⁵ The oxidative cyclisation of compounds **1-10** to **11-20** were accompanied by the disappearance of the absorption maxima at 3150-3300 cm⁻¹, which are ascribed to the vibrations of NH group of the benzimidazole ring; at the same time the appearance of a new maximum at 1360-1388 cm⁻¹, which is characteristic for benzimidazoquinazoline ring with a tertiary nitrogen atom, appears.^{23,36}

The ¹H NMR spectra of the compound **A** as well as its derivatives have been recorded in CDCl₃/DMSO-*d*₆ using TMS as internal standard. In the spectra of 2-(*o*-aminophenyl) benzimidazole (**A**), signals at δ 6.4 and δ 8.25 ppm were appeared corresponding to free amino and imidazolyl protons respectively.^{33,35} The aromatic protons of various environments present in all compounds appeared as multiplets in the range of δ 6.84-8.81 ppm.^{35,37} ¹H NMR spectra of compounds **1-10** contain signals corresponding to CH=N protons in the range of δ 8.07-8.29 ppm suggesting the condensation of aromatic aldehydes with compound **A**. However, in the spectra of **1-10** compounds the disappearance of signals at δ 6.4 ppm which is due to NH₂ protons of compound **A** supports the involvement of amino group in condensation and confirms the formation of azomethines. Finally, in the spectra of **11-20** compounds disappearance of signals corresponding to –NH of imidazolyl ring and CH=N protons supports the benzimidazoquinazoline ring structure.^{23, 36}



Scheme 1. Synthesis of 6-arylbenzimidazo[1,2-*c*]quinazolines (**11-20**).

¹³C NMR spectra of all the compounds contain signals in the range of δ 141.1-171.2 ppm confirming the presence of carbon, which is doubly bonded to nitrogen. The aromatic carbons of various environments present in all the compounds appeared as signals in the range of δ 103.2-156.2 ppm.³⁷ The ¹H and ¹³C NMR spectra (Figure S2 and Figure S3) of compound **20** are given in supplementary material.

All the compounds (except **2** and **12**) showed a single peak in ESI-MS suggesting the molecular formulae of the azomethines and quinazolines. Compounds, **2** and **12** exhibited molecular ion peaks (M^+) at m/z 391, (M^{+2}) at m/z 393 and (M^+) at m/z 389, (M^{+2}) at m/z 391 respectively, which is due to the isotopic abundance of bromine. The FAB mass spectrum of compound **20** shows a molecular ion peak (M^+) at m/z 296 (65.1%), which confirms the proposed formula ($C_{19}H_{12}N_4$). The peaks have been observed at m/z values 218 (40.3%), 193 (52.2%), 192 (100%), 180 (74.8%) and 76 (24.4%), which indicate the fragmentation pattern and their intensity gives an idea about the abundance and stability of the fragments. The mass fragmentation pattern (Scheme S1) of compound **20** as assigned on the basis of mass spectra (Figure S3) is presented in supplementary material.

Biological study

Antimicrobial activity

The *in vitro* antimicrobial activity was carried out by cup-plate method.³⁸ All the synthesized quinazolines were screened for antibacterial activity against *Staphylococcus aureus*,

Bacillus subtilis, *Streptococcus pyogenes* (Gram positive) and *Salmonella typhimurium*, *Escherichia coli*, *Klebsiella pneumonia* (Gram negative) bacterial strains using ampicillin as standard. The antifungal activity was investigated against *Aspergillus niger*, *Candida albicans*, *Trichoderma viridae* fungal strains using ketoconazole as standard. Preliminary screening of target compounds and standard drugs were performed at fixed concentrations of 1000 $\mu\text{g mL}^{-1}$. Inhibition was recorded by measuring the diameter of the inhibition zone at the end of 48 h for bacteria and 72 h for fungi. Each experiment was repeated thrice and the average of the three independent determinations was recorded. Screening results are summarized in Table 1. Among the compounds tested **13** was found to exhibit good activity against all bacterial and fungal strains. Furthermore, the most potent activity was observed in **19** and **20** against all bacterial and fungal strains when compared to respective standard drugs ampicillin and ketoconazole. The minimum inhibitory concentration³⁹ of these quinazolines (**13**, **19** and **20**) was also verified by the liquid dilution method in which the effectiveness was observed at lower concentrations. The detailed antibacterial and antifungal preliminary screening methods are given in supplementary material.

Determination of minimum inhibitory concentration (MIC)

The minimum inhibitory concentration of **13**, **19** and **20** against *S. aureus*, *B. subtilis*, *S. pyogenes*, *S. typhimurium*, *E. coli*, *K. pneumonia* (bacterial strains), *Aspergillus niger*, *Candida albicans*, *Trichoderma viridae* (fungal strains) were determined by liquid dilution method. Stock solutions of test samples with 2.5, 5, 10, 15, 20, 25, 30,

Table 1. Zone of inhibition of newly synthesized 6-arylbenzimidazo[1,2-c]quinazolines (**11-20**) against different bacteria and fungi

Compound (1000 $\mu\text{g mL}^{-1}$)	Zone of inhibition (mm)								
	Gram-positive bacteria				Gram-negative bacteria			Fungi	
	<i>S. aureus</i>	<i>B. subtilis</i>	<i>S. pyogenes</i>	<i>S. typhimurium</i>	<i>E. coli</i>	<i>K. pneumonia</i>	<i>A. niger</i>	<i>C. albicans</i>	<i>T. viridae</i>
11	20	18	13	15	18	16	21	16	9
12	21	20	15	15	19	18	18	15	12
13	50	45	48	45	48	50	49	48	46
14	19	14	15	12	21	15	16	13	13
15	22	18	13	16	18	12	15	10	9
16	18	14	15	12	20	16	16	12	13
17	16	18	15	15	19	18	18	15	12
18	15	10	12	10	9	13	11	9	13
19	55	45	52	50	50	52	55	50	50
20	52	48	50	46	51	50	50	51	48
Std	48 ^a	39 ^a	35 ^a	45 ^a	40 ^a	45 ^a	45 ^b	40 ^b	41 ^b

^a Ampicillin; ^b Ketoconazole

35, 40, 45 and 50 $\mu\text{g mL}^{-1}$ concentrations were prepared with appropriate solvent. The solutions of standard drugs, ampicillin and ketoconazole were prepared in the same concentrations. Inoculums of the bacterial and fungal culture were also prepared. To a series of tubes containing 1 mL each of quinazoline compound solution with different concentrations and 0.2 mL of the inoculum was added. Further 3.8 mL of the sterile water was added to each of the test tubes. These test tubes were incubated for 24 h and observed for the presence of turbidity. This method was repeated by changing quinazoline compounds with standard drug ampicillin (in case of bacteria) and with ketoconazole (in case of fungi) for comparison. The minimum inhibitory concentration at which no growth was observed was taken as the MIC values. Comparison of MIC values (in $\mu\text{g mL}^{-1}$) of quinazolines and standard drugs against different bacteria and fungi are presented in Figure 1. From these results, it is evident that **13** (MIC range 5-20 $\mu\text{g mL}^{-1}$), **19** and **20** compounds (MIC range 2.5-15 $\mu\text{g mL}^{-1}$) are showing superior activity when compared to ampicillin

and ketoconazole towards inhibiting all tested bacterial and fungal strains.

Conclusions

Quinazolines and related derivatives are classes of heterocyclic compounds contain the pyrimidine nucleus in their structures. Literature survey reveals that a variety of antimicrobial agents contains quinazoline moiety and also fused quinazoline ring systems such as benzimidazoloquinazolines, indoloquinazolines and many other. In a search for new fused quinazoline systems with potential biological activities, we planned to prepare new 6-arylbenzimidazo[1,2-c]quinazolines, from 2-(*o*-aminophenyl) benzimidazole and various aldehydes as starting compounds. We have chosen six bacterial and three fungal strains for microbial studies of these entire quinazoline compounds. From this study it is evident that all quinazoline compounds are showing moderate to good activity towards inhibiting all tested bacterial

Table 2 . MIC values potent 6-arylbenzimidazo[1,2-c]quinazolines (**13**, **19** and **20**) and standard drugs

Compound	Range of concentration ($\mu\text{g mL}^{-1}$)								
	Gram-positive bacteria			Gram-negative bacteria			Fungi		
	<i>S. aureus</i>	<i>B. subtilis</i>	<i>S. pyogenes</i>	<i>S. typhimurium</i>	<i>E. coli</i>	<i>K. pneumonia</i>	<i>A. niger</i>	<i>C. albicans</i>	<i>T. viridae</i>
13	10	15	20	10	15	5	10	20	15
19	2.5	15	10	5	10	2.5	2.5	5	10
20	5	10	15	10	10	5	10	15	15
Std	10 ^a	20 ^a	25 ^a	10 ^a	15 ^a	10 ^a	15 ^b	25 ^b	20 ^b

^a Ampicillin; ^b Ketoconazole

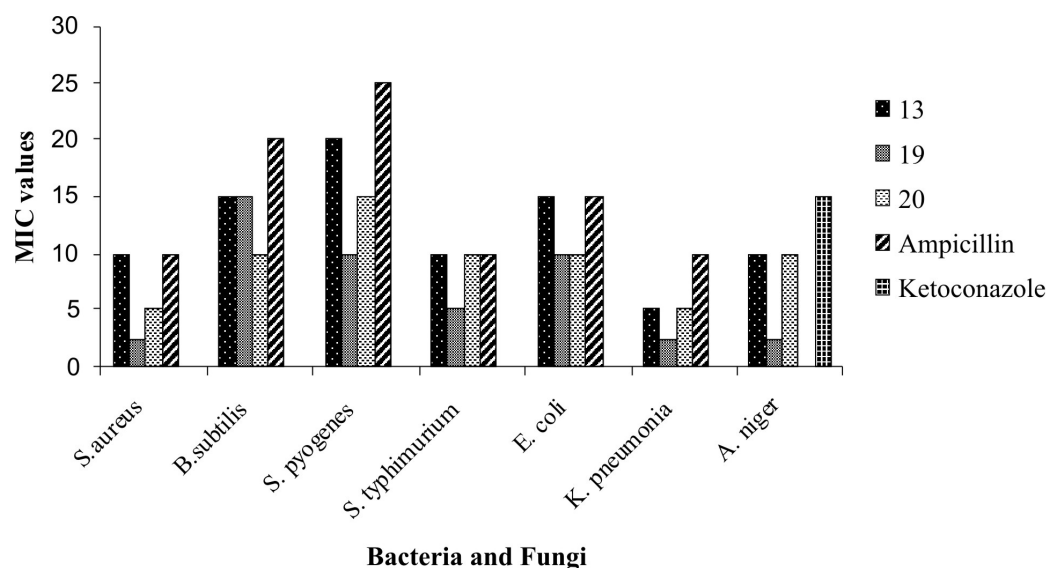


Figure 1. Comparison of MIC values (in $\mu\text{g mL}^{-1}$) of quinazolines and standard drugs against different bacteria and fungi.

and fungal strains. Furthermore, the most potent activity was observed in (**13**, **19** and **20**) against all bacterial and fungal strains when compared to respective standard drugs ampicillin and ketoconazole. A possible explanation for this result is that the biological activity of compounds may be depending on the basic skeleton of molecule as well as on the nature of substituents. Hence we conclude that the most potent activity of **13**, **19** and **20** compounds may be due to the presence of heterocyclic isoquinolyl, pyridyl and nitro substituted aryl groups at C₆ position of the benzimidazo[1,2-c]quinazoline moiety.

Experimental

Analar grade reagents and freshly distilled solvents were used throughout the investigations. Compounds were checked for their purity by TLC using Merck 60 F₂₅₄ silica gel plates and spots were located by iodine vapors. Micro analytical (C, N, H) data was obtained by using a Perkin-Elmer 2400 CHN elemental analyzer. The IR spectra were recorded in KBr pellets on Perkin-Elmer-283 spectrophotometer. ¹H NMR spectra were acquired at 400 MHz and ¹³C NMR was acquired at 67.93 MHz on a Bruker NMR spectrometer. FAB mass spectra were recorded on a Finnigan-MAT 1020 instrument. An ion trap mass spectrometer (Agilent Series LC/MSD Trap SL) equipped with an electrospray ionization (ESI) source was used for MS analyses. Hot air oven (Instrument and Equipment Pvt. Ltd., Mumbai), incubator (Instrument and Equipment Pvt. Ltd., Mumbai), laminar airflow unit (Clas laminar technologies Pvt. Ltd. Secunderabad), autoclave (Medica Instrument Mfg. Co., Mumbai) were used in the present investigations. Organisms like *Staphylococcus aureus*, *Bacillus subtilis*, *Streptococcus pyogenes* (Gram positive), *Salmonella typhimurium*, *Escherichia coli*, *Klebsiella pneumonia* (Gram negative) bacteria and *Aspergillus niger*, *Candida albicans*, *Trichoderma viridae* fungi were used in the present investigations.

Preparation of 2-(*o*-aminophenyl)benzimidazole [BIPhNH₂] (A)

2-(*o*-aminophenyl) benzimidazole (A) was prepared by reacting orthophenylenediamine (OPD) with anthranillic acid in freshly prepared polyphosphoric acid (PPA) acid at 250 °C for 4 h.

Procedure for preparation of mono-2-(*o*-arylideneamino) phenyl benzimidazoles (**1-10**)

To a hot stirred solution of 2-(*o*-aminophenyl) benzimidazole (A) (2 mmol) in ethanol (20 mL) were

added the appropriate aldehyde (2 mmol) and 2-3 drops of acetic acid. The resultant mixture was refluxed under heat (40-55 °C) for 2 h after which the compound was obtained. The product was filtered and recrystallized from a dichloromethane-methanol mixture.

Procedure for preparation of 6-arylbenzimidazo[1,2-c]quinazolines[BIQ-Ar] (**11-20**)

All the 6-arylbenzimidazo[1,2-c]quinazolines (**11-20**) were prepared from azomethines **1-10** through oxidative cyclisation method reported by Davis and Mann.³² Powdered potassium permanganate (1.5 equiv.) was added to a solution of the azomethyne compound (**1-10**) in 50-75 mL of acetone. The mixture was boiled (40-80 °C) under reflux for 30 min. It was then filtered hot, and an equal volume of hot water added to the filtrate. The quinazolines (**11-20**) rapidly separated, and was collected by filtration and recrystallized from dimethylformamide. All the synthesized compounds were characterized as given below.

2-(*o*-Aminophenyl)benzimidazole [BIPhNH₂] (A)

Yield 82%; mp 213-214°C (lit. 214°C);³¹ IR ν_{max}/cm⁻¹: 3350 (NH₂), 3300 (NH); ¹H NMR (400 MHz, CDCl₃) δ 6.4 (s, 2H, NH₂), 6.5-7.7 (m, 8H, Ar-H), 8.25 (s, 1H, NH); ¹³C NMR (67.93 MHz, CDCl₃) δ 113.1, 114.2, 116.2, 119.3, 121.5, 123.2, 130.3, 141.5, 145.2, 154.1 (13C, Ar-C). Anal. Found: C, 74.65; H, 5.32; N, 20.05. Calc. for C₁₃H₁₁N₃: C, 74.62; H, 5.30; N, 20.08%. MS (ESI): (M⁺) *m/z* at 209.

2-([2-(1*H*-Benzo[*d*]imidazol-2-yl)phenyl]iminomethyl) phenol (1)

Yield 81%; mp 288-290 °C; IR ν_{max}/cm⁻¹: 3420, 3300, 1650, 1590, 1575, 1130; ¹H NMR (400 MHz, CDCl₃) δ 6.83 (t, 1H, Ar, *J* 7.4Hz), 6.95-7.38 (m, 9H, Ar), 7.63-7.95 (m, 2H, Ar), 8.25 (s, 1H, CH=N), 8.89 (s, 1H, imidazolyl-NH) 10.22 (s, 1H, -OH); ¹³C NMR (67.93 MHz, CDCl₃) δ 114.3, 117.2, 118.4, 123.5, 126.4, 131.5, 132.2, 133.6, 136.5, 141.2, 142.6, 143.8, 146.3, 163.7, 167.5 (20C, Ar-C); Anal. Found: C, 76.65; H, 4.81; N, 13.40. Calc. for C₂₀H₁₅N₃O: C, 76.66; H, 4.82; N, 13.41%. MS (ESI): (M⁺) *m/z* at 313.

2-([2-(1*H*-Benzo[*d*]imidazol-2-yl)phenyl]iminomethyl)-4-bromophenol (2)

Yield 79%; mp 318-320 °C; IR ν_{max}/cm⁻¹: 3425, 3300, 1630, 1610, 1580, 1100; ¹H NMR (400 MHz, CDCl₃) δ 6.82 (t, 1H, Ar, *J* 7.4 Hz), 6.85 (s, 1H, Ar), 6.92-7.46 (m, 7H, Ar), 7.62 -7.94 (m, 2H, Ar), 8.21 (s, 1H, CH=N), 8.86 (s, 1H, -NH), 10.21 (s, 1H, -OH); ¹³C NMR (67.93 MHz, CDCl₃) δ 107.5, 114.1, 118.2, 123.5, 126.2, 130.5, 131.2, 132.2, 136.5, 141.1, 142.8, 143.5, 146.3, 154.48, 158.5, 167.1

(20C, Ar-C); Anal. Found: C, 61.20; H, 3.56; N, 10.71. Calc. for $C_{20}H_{14}BrN_3O$: C, 61.24; H, 3.60; N, 10.71%. MS (ESI): (M^+) m/z (%) 391, (M^+) m/z at 393.

2-([2-(1*H*-Benzo[d]imidazol-2-yl)phenyl]iminomethyl)-4-nitrophenol (**3**)

Yield 81%; mp 255-257 °C; IR ν_{max}/cm^{-1} : 3420, 3300, 1635, 1608, 1590, 1525, 1345, 1130, 850; 1H NMR (400 MHz, $CDCl_3$) δ 6.82 (t, 1H, Ar, *J* 7.4 Hz), 7.05-7.41 (m, 6H, Ar), 7.60 (s, 1H, Ar), 7.63-7.95 (m, 2H, Ar), 8.01 (d, 1H, *J* 7.7 Hz), 8.29 (s, 1H, CH=N), 8.85 (s, 1H, -NH), 10.45 (s, 1H, -OH); ^{13}C NMR (67.93 MHz, $CDCl_3$) δ 114.4, 118.1, 119.2, 123.1, 124.3, 126.2, 131.2, 132.2, 136.5, 141.1, 143.5, 146.5, 164.8, 170.2 (20C, Ar-C); Anal. Found: C, 67.01; H, 3.95; N, 15.58. Calc. for $C_{20}H_{14}N_4O_3$: C, 67.03; H, 3.94; N, 15.63%. MS (ESI): (M^+) m/z at 358.

2-([2-(1*H*-Benzo[d]imidazol-2-yl)phenyl]iminomethyl)-4-methoxyphenol (**4**)

Yield 80%; mp 285-287 °C; IR ν_{max}/cm^{-1} : 3425, 3300, 1638, 1605, 1585, 1246, 1128, 1035; 1H NMR (400 MHz, $CDCl_3$) δ 3.90 (s, 3H, OCH_3), 6.48 (s, 1H, Ar), 6.83 (t, 1H, Ar, *J* 7.4 Hz), 6.84-7.65 (m, 8H, Ar), 7.94 (d, 1H, Ar, *J* 7.3 Hz), 8.16 (s, 1H, CH=N), 8.85 (s, 1H, -NH), 10.22 (s, 1H, -OH); ^{13}C NMR (67.93 MHz, $CDCl_3$) δ 56.1, (1C, $-OCH_3$), 114.0, 121.5, 122.4, 123.5, 126.2, 130.5, 131.1, 132.4, 141.1, 142.3, 146.8, 153.2, 153.6, 167.5 (20C, Ar-C); Anal. Found: C, 73.42; H, 5.01; N, 12.25. Calc. for $C_{21}H_{17}N_3O_2$: C, 73.45; H, 4.99; N, 12.24 %. MS (ESI): (M^+) m/z 343.

3-([2-(1*H*-Benzo[d]imidazol-2-yl)phenyl]iminomethyl)benzoic acid (**5**)

Yield 76%; mp 226-228 °C; IR ν_{max}/cm^{-1} : 3535, 3300, 3215, 1685, 1635, 1580, 1130; 1H NMR (400 MHz, $CDCl_3$) δ 6.83 (t, 1H, Ar, *J* 7.4 Hz), 7.05-8.20 (m, 12H, Ar), 8.82 (s, 1H, -NH), 11.31 (s, 1H, -COOH); ^{13}C NMR (67.93 MHz, $CDCl_3$) δ 114.1, 114.4, 123.5, 126.2, 129.2, 130.5, 130.8, 132.0, 133.1, 141.1, 143.5, 146.8, 167.1, 170.2 (21C, Ar-C); Anal. Found: C, 73.85; H, 4.49; N, 12.32. Calc. for $C_{21}H_{15}N_3O_2$: C, 73.89; H, 4.43; N, 12.31%. MS (ESI): (M^+) m/z 341.

3-([2-(1*H*-Benzo[d]imidazol-2-yl)phenyl]iminomethyl)-4-hydroxybenzoic acid (**6**)

Yield 79%; mp 315-317 °C; IR ν_{max}/cm^{-1} : 3535, 3425, 3300, 3215, 1680, 1640, 1585, 1128; 1H NMR (400 MHz, $CDCl_3$) δ 6.83 (t, 1H, Ar, *J* 7.4 Hz), 7.02-8.13 (m, 11H, Ar), 8.89 (s, 1H, -NH), 10.21 (s, 1H, -OH), 11.42 (s, 1H, -COOH); ^{13}C NMR (67.93 MHz, $CDCl_3$) δ 113.6, 114.0, 114.3, 123.4, 124.5, 126.2, 127.5, 132.8, 136.4, 141.1, 142.3, 144.5, 146.1, 166.2, 166.7, 168.8 (21C, Ar-C); Anal.

Found: C, 70.60; H, 4.25; N, 11.70. Calc. for $C_{21}H_{15}N_3O_3$: C, 70.58; H, 4.23; N, 11.76%. MS (ESI): (M^+) m/z 357.

4-([2-(1*H*-Benzo[d]imidazol-2-yl)phenyl]iminomethyl)-2,6-dimethylphenol (**7**)

Yield 78%; mp 211-213 °C; IR ν_{max}/cm^{-1} : 3425, 3300, 2958, 1645, 1608, 1575, 1130; 1H NMR (400 MHz, $CDCl_3$) δ 2.30 (s, 6H, Ar- CH_3), 6.61 (s, 2H, Ar), 6.83 (t, 1H, Ar, *J* 7.4 Hz), 7.06-7.41 (m, 5H, Ar), 7.62-7.93 (m, 2H, Ar), 8.07 (s, 1H, CH=N), 8.85 (s, 1H, -NH), 10.21 (s, 1H, -OH); ^{13}C NMR (67.93 MHz, $CDCl_3$) δ 15.7 (2C, $-CH_3$), 114.1, 123.4, 126.2, 127.4, 128.3, 132.2, 136.3, 141.1, 146.6, 152.8, 171.2 (20C, Ar-C); Anal. Found: C, 77.44; H, 5.60; N, 12.29. Calc. for $C_{22}H_{19}N_3O$: C, 77.40; H, 5.61; N, 12.31%. MS (ESI): (M^+) m/z 341.

*N*1-[(*E*)-1-(3,5-Dimethoxyphenyl)methylidene]-2-(1*H*-benzo[d]imidazol-2-yl) aniline (**8**)

Yield 75%; mp 228-230 °C; IR ν_{max}/cm^{-1} : 3300, 1635, 1600, 1580, 1246, 1130, 1035; 1H NMR (400 MHz, $CDCl_3$) δ 3.90 (s, 6H, $-OCH_3$), 6.46 (s, 1H, Ar), 6.82 (t, 1H, Ar, *J* 7.4 Hz), 6.85 (s, 2H, Ar), 7.08-7.45 (m, 5H, Ar), 7.62-7.94 (m, 2H, Ar), 8.14 (s, 1H, CH=N), 8.89 (s, 1H, -NH); ^{13}C NMR (67.93 MHz, $CDCl_3$) δ 55.2 (2C, $-OCH_3$), 103.9, 108.1, 114.0, 114.2, 123.6, 127.3, 131.2, 132.2, 134.3, 141.1, 146.6, 162.3, 168.3 (20C, Ar-C); Anal. Found: C, 73.92; H, 5.35; N, 11.76. Calc. for $C_{22}H_{19}N_3O_2$: C, 73.93; H, 5.36; N, 11.76%. MS (ESI): (M^+) m/z 357.

*N*1-[(*E*)-1-(1-Isoquinolyl)methylidene]-2-(1*H*-benzo[d]imidazol-2-yl)aniline (**9**)

Yield 81%; mp 254-256 °C; IR ν_{max}/cm^{-1} : 3300, 1640, 1610, 1580, 1130; 1H NMR (400 MHz, $CDCl_3$) δ 6.83 (t, 1H, Ar, *J* 7.4 Hz), 7.06-8.21 (m, 13H, Ar), 8.72 (d, 1H, *J* 5.25 Hz), 8.89 (s, 1H, -NH); ^{13}C NMR (67.93 MHz, $CDCl_3$) δ 114.0, 114.2, 121.6, 123.4, 125.6, 127.3, 128.8, 132.6, 135.6, 141.8, 146.8, 157.2, 168.4 (23C, Ar-C); Anal. Found: C, 79.25; H, 4.60; N, 16.05. Calc. for $C_{23}H_{16}N_4$: C, 79.29; H, 4.63; N, 16.08%. MS (ESI): (M^+) m/z 348.

*N*1-[(*E*)-1-(3-Pyridyl)methylidene]-2-(1*H*-benzo[d]imidazol-2-yl)aniline (**10**)

Yield 79%; mp 230-232 °C; IR ν_{max}/cm^{-1} : 3300, 1640, 1610, 1585, 1130; 1H NMR (400 MHz, $CDCl_3$) δ 6.82 (t, 1H, Ar, *J* 7.4 Hz), 7.05-7.48 (m, 6H, Ar), 7.63 (d, 1H, Ar, *J* 7.3 Hz), 7.75-8.62 (m, 4H, Ar), 8.65 (s, 1H, Ar), 8.89 (s, 1H, -NH); ^{13}C NMR (67.93 MHz, $CDCl_3$) δ 113.4, 114.1, 121.5, 123.4, 126.3, 128.3, 130.3, 136.5, 141.8, 143.6, 146.5, 151.6, 152.8, 165.6 (19 C, Ar-C); Anal. Found: C, 76.50; H, 4.72; N, 18.75. Calc. for $C_{19}H_{14}N_4$: C, 76.49; H, 4.73; N, 18.78%. MS (ESI): (M^+) m/z 298.

2-Benzo[4,5]imidazo[1,2-c]quinazolin-6-ylphenol (11)

Yield 82%; mp 300-302 °C; IR ν_{\max} /cm⁻¹: 3425, 1621, 1585, 1529, 1457, 1380, 773, 741, 732; ¹H NMR (400 MHz, DMSO-d₆) δ 6.65 (d, 1H, Ar, *J* 8.2 Hz), 6.81 (d, 1H, Ar, *J* 8.4 Hz), 6.83 (t, 1H, Ar, *J* 7.4 Hz), 7.15-7.85 (m, 8H, Ar), 8.75 (dd, 1H, *J* 6.9, 2.5 Hz), 10.29 (s, 1H, -OH); ¹³C NMR (67.93 MHz, DMSO-d₆) δ 112.4, 116.7, 120.3, 121.5, 122.4, 125.8, 129.3, 131.5, 132.7, 139.2, 143.6, 152.5, 159.2, 161.4 (20 C, Ar-C); Anal. Found: C, 77.18; H, 4.19; N, 13.51. Calc. for C₂₀H₁₃N₃O: C, 77.16; H, 4.21; N, 13.50%. MS (ESI): (M⁺) at *m/z* 311.

2-Benzo[4,5]imidazo[1,2-c]quinazolin-6-yl-4-bromophenol (12)

Yield 75%; mp 330-332 °C; IR ν_{\max} /cm⁻¹: 3425, 1621, 1610, 1524, 1459, 1378, 775, 744, 739; ¹H NMR (400 MHz, DMSO-d₆) δ 6.65 (d, 1H, Ar, *J* 8.2 Hz), 6.81 (d, 1H, Ar, *J* 8.4 Hz), 6.82 (t, 1H, Ar, *J* 7.4 Hz), 7.15-7.56 (m, 6H, Ar), 7.75 (s, 1H, Ar), 8.75 (dd, 1H, *J* 6.9, 2.5 Hz), 10.30 (s, 1H, -OH); ¹³C NMR (67.93 MHz, DMSO-d₆) δ 111.4, 118.2, 120.1, 121.5, 122.3, 125.8, 130.7, 131.5, 132.6, 133.2, 145.6, 146.5, 152.8, 154.5, 161.2 (20 C, Ar-C); Anal. Found: C, 61.55; H, 3.12; N, 10.75. Calc. for C₂₀H₁₂BrN₃O: C, 61.56; H, 3.10; N, 10.77%. MS (ESI): at *m/z* (M⁺) 389, (M²⁺) 391.

2-Benzo[4,5]imidazo[1,2-c]quinazolin-6-yl-4-nitrophenol (13)

Yield 76%; mp 241-243 °C; IR ν_{\max} /cm⁻¹: 3425, 1640, 1605, 1580, 1520, 1459, 1385, 851, 775, 745, 749, 690; ¹H NMR (400 MHz, DMSO-d₆) δ 6.64 (d, 1H, Ar, *J* 8.2 Hz), 6.82 (d, 1H, Ar, *J* 8.4 Hz), 6.83 (t, 1H, Ar, *J* 7.4 Hz), 7.21-8.15 (m, 6H, Ar), 8.45 (s, 1H, Ar), 8.74 (dd, 1H, *J* 6.9, 2.5 Hz), 10.29 (s, 1H, -OH); ¹³C NMR (67.93 MHz, DMSO-d₆) δ 112.4, 118.3, 120.6, 121.7, 124.8, 125.4, 126.8, 130.7, 132.3, 138.4, 143.6, 145.4, 152.1, 163.2, 164.5 (20C, Ar-C); Anal. Found: C, 67.42; H, 3.40N, 15.71. Calc. for C₂₀H₁₂N₄O₃: C, 67.41; H, 3.39N, 15.72%. MS (ESI): (M⁺) at *m/z* 356.

2-Benzo[4,5]imidazo[1,2-c]quinazolin-6-yl-4-methoxyphenol (14)

Yield 81%; mp 300-302 °C; IR ν_{\max} /cm⁻¹: 3425, 1638, 1615, 1575, 1465, 1380, 1245, 1038, 770, 742, 739; ¹H NMR (400 MHz, DMSO-d₆) δ 3.91 (s, 3H, Ar-OCH₃), 6.65 (d, 1H, Ar, *J* 8.2 Hz), 6.82 (d, 1H, Ar, *J* 8.4 Hz), 6.83 (t, 1H, Ar, *J* 7.4 Hz), 6.98-7.53 (m, 7H, Ar), 8.76 (dd, 1H, *J* 6.9, 2.5 Hz), 10.29 (s, 1H, -OH); ¹³C NMR (67.93 MHz, DMSO-d₆) δ 56.3 (1C, -OCH₃), 112.3, 119.6, 121.7, 122.7, 124.8, 127.8, 130.7, 131.2, 137.2, 143.6, 152.2, 155.6, 160.3 (20C, Ar-C); Anal. Found: C, 73.85; H, 4.41; N,

12.30. Calc. for C₂₁H₁₅N₃O₂: C, 73.89; H, 4.43; N, 12.31%. MS (ESI): (M⁺) at *m/z* 341.

3-Benzo[4,5]imidazo[1,2-c]quinazolin-6-ylbenzoic acid (15)

Yield 75%; mp 238-240 °C; IR ν_{\max} /cm⁻¹: 3535, 1685, 1621, 1585, 1529, 1457, 1380, 773, 741, 732; ¹H NMR (400 MHz, DMSO-d₆) δ 6.64 (d, 1H, Ar, *J* 8.2 Hz), 6.82 (d, 1H, Ar, *J* 8.4 Hz), 6.83 (t, 1H, Ar, *J* 7.4 Hz), 7.21-8.31 (m, 7H, Ar), 8.63 (s, 1H, Ar), 8.75 (dd, 1H, *J* 6.9, 2.5 Hz), 11.34 (s, 1H, -COOH); ¹³C NMR (67.93 MHz, DMSO-d₆) δ 111.6, 114.6, 120.9, 122.8, 124.6, 126.3, 129.7, 131.8, 132.5, 142.6, 143.1, 152.1, 157.8, 167.2 (21C, Ar-C); Anal. Found: C, 74.31; H, 3.85; N, 12.39. Calc. for C₂₁H₁₃N₃O₂: C, 74.33; H, 3.86; N, 12.38%. MS (ESI): (M⁺) at *m/z* 339.

3-Benzo[4,5]imidazo[1,2-c]quinazolin-6-yl-4-hydroxybenzoic acid (16)

Yield 78%; mp 342-344 °C; IR ν_{\max} /cm⁻¹: 3535, 3425, 1680, 1621, 1585, 1529, 1457, 1388, 773, 740, 738; ¹H NMR (400 MHz, DMSO-d₆) δ 6.65 (d, 1H, Ar, *J* 8.2 Hz), 6.81 (d, 1H, Ar, *J* 8.4 Hz), 6.83 (t, 1H, Ar, *J* 7.4 Hz), 7.20-8.15 (m, 6H, Ar), 8.49 (s, 1H, Ar), 8.75 (dd, 1H, *J* 6.9, 2.5 Hz), 10.21 (s, 1H, -OH), 11.30 (s, 1H, -COOH); ¹³C NMR (67.93 MHz, DMSO-d₆) δ 112.6, 117.7, 120.5, 121.7, 122.5, 128.7, 131.8, 135.5, 143.5, 143.2, 152.5, 161.3, 162.8, 165.2 (21C, Ar-C); Anal. Found: C, 70.95; H, 3.70; N, 11.80. Calc. for C₂₁H₁₃N₃O₃: C, 70.98; H, 3.69; N, 11.82%. MS (ESI): (M⁺) at *m/z* 355.

4-Benzo[4,5]imidazo[1,2-c]quinazolin-6-yl-2,6-dimethylphenol (17)

Yield 71%; mp 208-210 °C; IR ν_{\max} /cm⁻¹: 3425, 2958, 1680, 1621, 1585, 1529, 1457, 1388, 773, 741, 739; ¹H NMR (400 MHz, DMSO-d₆) δ 2.31 (s, 6H, -CH₃), 6.64 (d, 1H, Ar, *J* 8.2 Hz), 6.82 (d, 1H, Ar, *J* 8.4 Hz), 6.83 (t, 1H, Ar, *J* 7.4 Hz), 7.20-7.53 (m, 6H, Ar), 8.74 (dd, 1H, *J* 6.9, 2.5 Hz), 10.21 (s, 1H, -OH); ¹³C NMR (67.93 MHz, DMSO-d₆) δ 15.6 (2C, -CH₃), 112.8, 114.5, 121.9, 122.4, 124.6, 126.5, 128.7, 133.5, 145.1, 151.1, 152.5, 158.2, (20C, Ar-C); Anal. Found: C, 77.86; H, 5.01; N, 12.35. Calc. for C₂₂H₁₇N₃O: C, 77.86; H, 5.05; N, 12.38%. MS (ESI): (M⁺) at *m/z* 339.

6-(3,5-Dimethoxyphenyl)benzo[4,5]imidazo[1,2-c]quinazoline (18)

Yield 75%; mp 235-237 °C; IR ν_{\max} /cm⁻¹: 1645, 1605, 1528, 1456, 1246, 1380, 1038, 773, 741, 732; ¹H NMR (400 MHz, DMSO-d₆) δ 3.90 (s, 6H, -OCH₃), 6.54 (s, 1H, Ar), 6.65 (d, 1H, Ar, *J* 8.2 Hz), 6.81 (d, 1H, Ar, *J* 8.4 Hz), 6.83 (t, 1H, Ar, *J* 7.4 Hz), 7.20-7.51 (m, 4H, Ar), 7.68 (s, 2H,

Ar), 8.75 (dd, 1H, *J* 6.9, 2.5 Hz); ¹³C NMR (67.93 MHz, DMSO-d₆) δ 55.4 (2C, -OCH₃), 103.5, 104.7, 112.3, 120.3, 124.3, 126.9, 131.3, 133.4, 141.2, 143.8, 152.2, 155.2, 165.2 (20C, Ar-C); Anal. Found: C, 74.34; H, 4.83; N, 11.80. Calc. for C₂₂H₁₇N₃O₂: C, 74.35; H, 4.82; N, 11.82%. MS (ESI): (M⁺)^{at} *m/z* 355.

6-(1-Isoquinoly)benzo[4,5]imidazo[1,2-c]quinazoline (19)

Yield 72%; mp 274-276 °C; IR ν_{max}/cm⁻¹: 1631, 1610, 1585, 1529, 1457, 1380, 773, 741, 732; ¹H NMR (400 MHz, DMSO-d₆) δ 6.64 (d, 1H, Ar, *J* 8.2 Hz), 6.82 (d, 1H, Ar, *J* 8.4 Hz), 6.83 (t, 1H, Ar, *J* 7.4 Hz), 7.21-8.51 (m, 9H, Ar), 8.72 (d, 1H, *J* 5.25 Hz), 8.74 (dd, 1H, *J* 6.9, 2.5 Hz); ¹³C NMR (67.93 MHz, DMSO-d₆) δ 114.2, 116.5, 120.3, 121.5, 123.3, 126.6, 133.3, 136.2, 138.4, 141.2, 145.2, 152.2, 153.1, 153.8 (23C, Ar-C); Anal. Found: C, 79.72; H, 4.05; N, 16.18. Calc. for C₂₃H₁₄N₄: C, 79.75; H, 4.07; N, 16.17%. MS (ESI): (M⁺)^{at} *m/z* 346.

6-(3-Pyridyl)benzo[4,5]imidazo[1,2-c]quinazoline (20)

Yield 73%; mp 244-246 °C; IR ν_{max}/cm⁻¹: 1635, 1610, 1580, 1530, 1457, 1380, 775, 742, 731; ¹H NMR (400 MHz, DMSO-d₆) δ 6.65 (d, 1H, Ar, *J* 8.2 Hz), 6.82 (d, 1H, Ar, *J* 8.4 Hz), 6.83 (t, 1H, Ar, *J* 7.4 Hz), 7.11-8.12 (m, 7H, Ar), 8.61 (dd, 1H, *J* 6.9, 2.5 Hz), 8.95 (s, 1H, Ar); ¹³C NMR (67.93 MHz, DMSO-d₆) δ 113.5, 119.6, 120.7, 123.3, 126.2, 130.3, 132.6, 137.2, 142.2, 146.7, 149.4, 150.1, 152.1 (19C, Ar-C); Anal. Found: C, 77.01; H, 4.05; N, 18.90. Calc. for C₁₉H₁₂N₄: C, 77.01; H, 4.08; N, 18.91%. MS (ESI): (M⁺)^{at} *m/z* 296.

Supplementary Information

Spectral data of compounds are available free of charge at <http://jbcs.sbq.org.br>, as pdf file.

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Synthesis and Antimicrobial Activities of a New Class of 6-Arylbenzimidazo[1,2-c]quinazolines

Rondla Rohini,^a Kanne Shanker,^a P. Muralidhar Reddy^b and Vadde Ravinder^{a*}

^aDepartment of Chemistry, Kakatiya University, Warangal-506 009, A.P., India

^bDepartment of Chemistry, National Dong Hwa University, Hualien, Taiwan

Antibacterial activity

Antibacterial testing was performed by cup plate method.³⁸ Nutrient broth was prepared by dissolving peptone (0.5%), yeast extract (0.15%), beef extract (0.15%), sodium chloride (0.36%), and monopotassium phosphate (0.13%) in distilled water (100 mL). The pH of the solution was adjusted to 7.2 by adding sodium hydroxide solution (4%) and the resulting solution was autoclaved for 20 min at 15 psi. One day prior to the experiment, the cultures against *Staphylococcus aureus*, *Bacillus subtilis*, *Streptococcus pyogenes*, *Salmonella typhimurium*, *Escherichia coli* and *Klebsiella pneumonia* were inoculated in nutrient broth (inoculation medium) and incubated overnight at 37 °C. Nutrient agar medium was prepared by dissolving peptone (1%), yeast extract (0.6%), beef extract (0.5%), and sodium chloride (0.5%) in distilled water. The pH of the solution was adjusted to 7.2 by adding 4% aqueous sodium hydroxide solution. Agar (2.4%) was then added and the whole solution was autoclaved for 20 min at 15 psi. Preliminary screening for ten quinazolines was performed at fixed concentrations of 1000 µg mL⁻¹. Inoculation medium containing 24-hours grown culture was added aseptically to the nutrient medium and mixed thoroughly to get the uniform distribution. This solution was poured (25 mL in each dish) into Petri dishes and then allowed to attain room temperature. Thereafter, six millimeter wide bores were made on the agar using a borer. The solutions of test samples were added into each of the bores using a sterile tip with micropipette. Ampicillin was used as the standard and DMSO as the solvent control. The test samples and the standard were tested at a concentration of

1000 µg mL⁻¹. The plates were allowed to stand for 1 h in order to facilitate the diffusion of the drug solution. Then the plates were incubated at 37 °C for 48 h. The zones of inhibition against all the microorganisms were measured in millimeters.

Antifungal activity

The antifungal activity of quinazoline compounds were tested against the pathogenic fungi *Aspergillus niger*, *Candida albicans*, *Trichoderma viridae* by cup-plate method.³⁸ Nutrient agar medium was prepared by the same method as explained under evaluation of antibacterial activity. One and half day prior to the experiment, the fungal cultures of *Aspergillus niger*, *Candida albicans* and *Trichoderma viridae* prepared in the inoculation medium were incubated at 37 °C for 36 h. The fungal medium was prepared by dissolving peptone (0.5%), sodium chloride (0.36%), monopotassium phosphate (0.13%), and glucose (2%) in distilled water (100 mL). The pH of the solution was adjusted to 7.2 by adding sodium hydroxide solution (4%) and the resulting solution was autoclaved for 20 min at 15 psi. This was cooled to 45-50 °C with gentle shaking. One and half day, grown cultures were added aseptically to this medium and mixed thoroughly to get uniform distribution. The solutions of the test samples and standard were evaluated for antifungal activity by cup-plate method at a concentration of 1000 µg. The zone of inhibition was measured in millimeter for the particular test sample with each organism at 72 h interval. Ketoconazole was used as the standard.

*e-mail: ravichemku@rediffmail.com

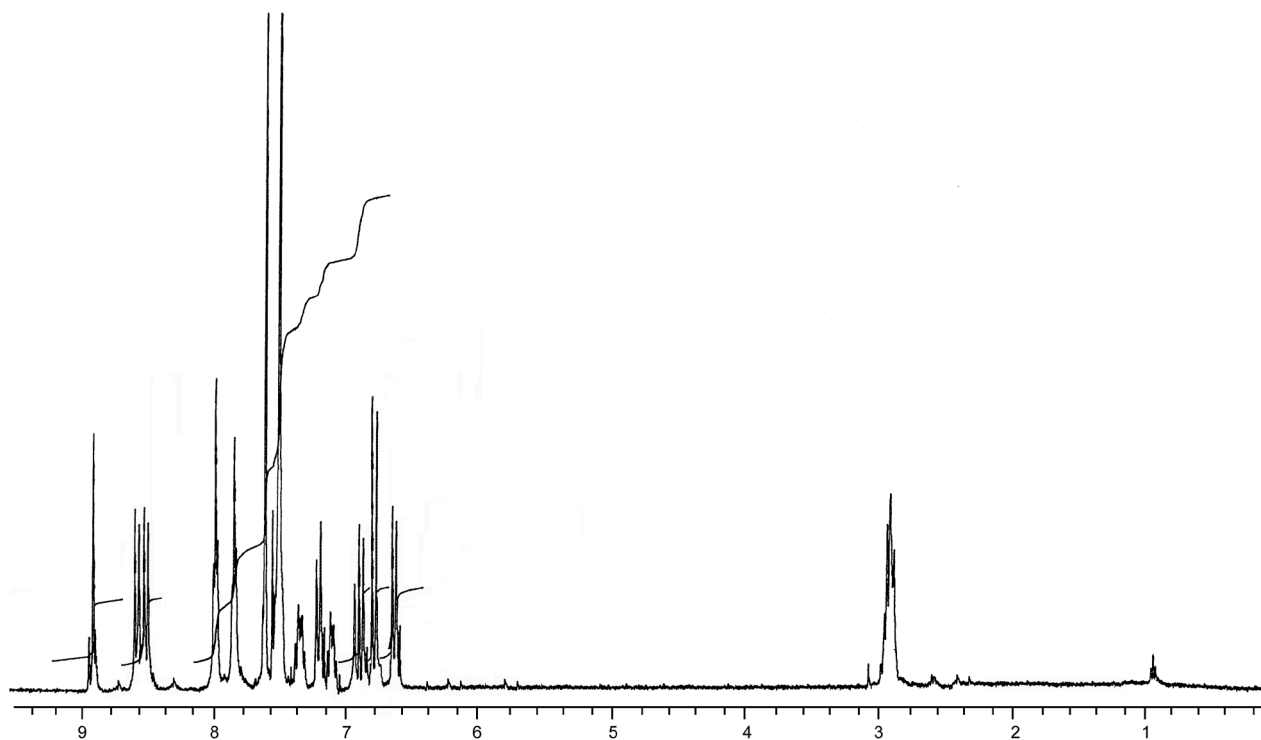


Figure S1. ^1H NMR spectrum of 6-(3-pyridyl)benzo[4,5]imidazo[1,2-*c*]quinazoline (**20**).

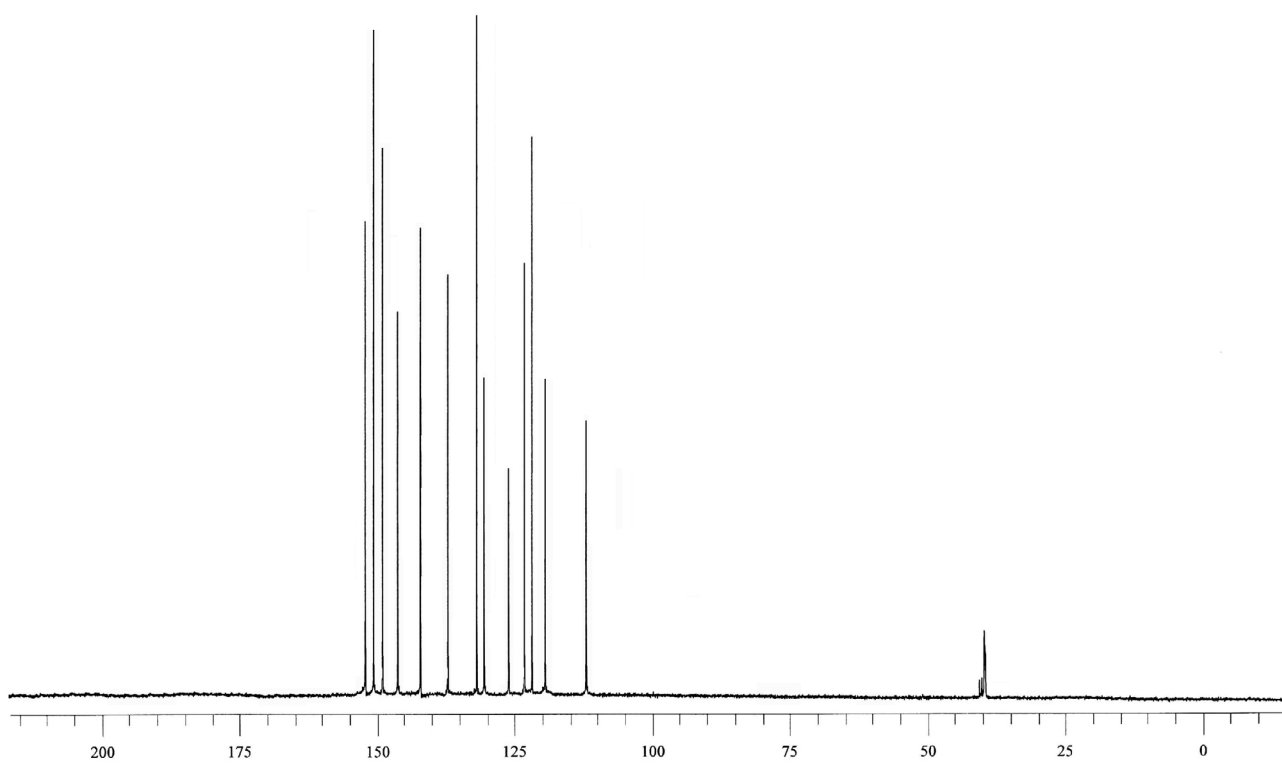


Figure S2. ^{13}C NMR spectrum of 6-(3-pyridyl)benzo[4,5]imidazo[1,2-*c*]quinazoline (**20**).

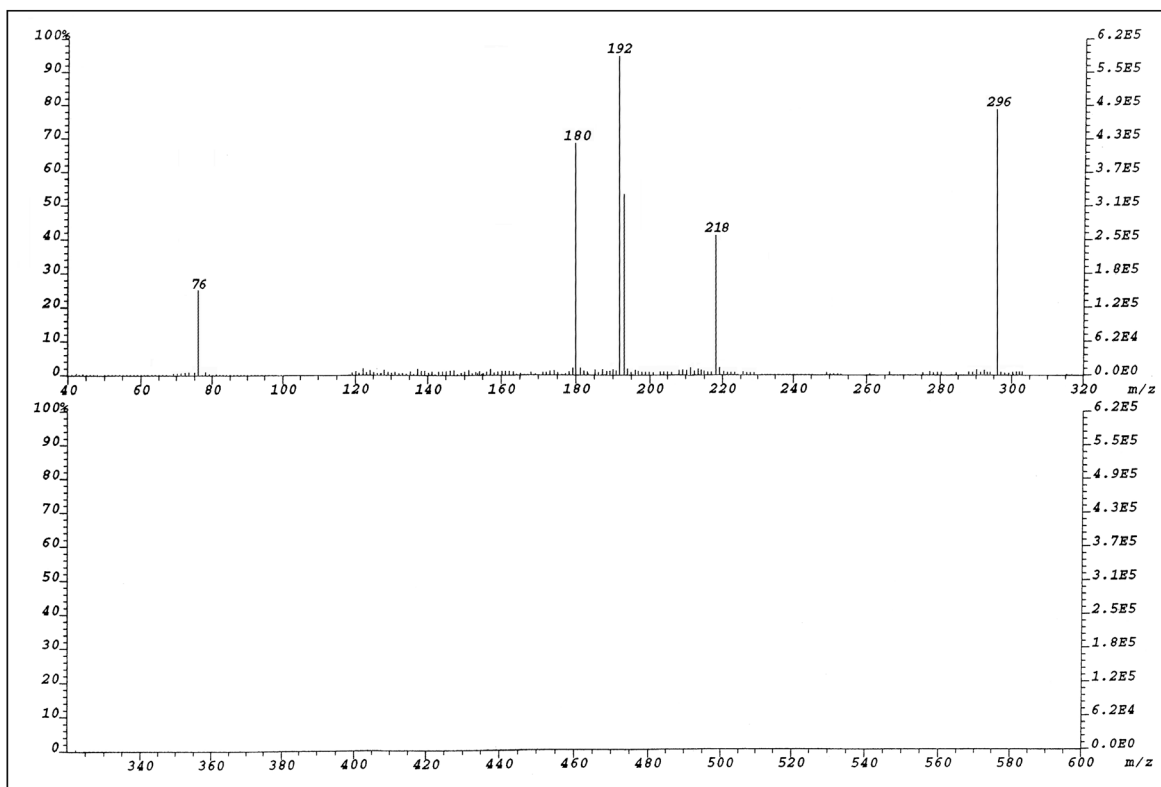
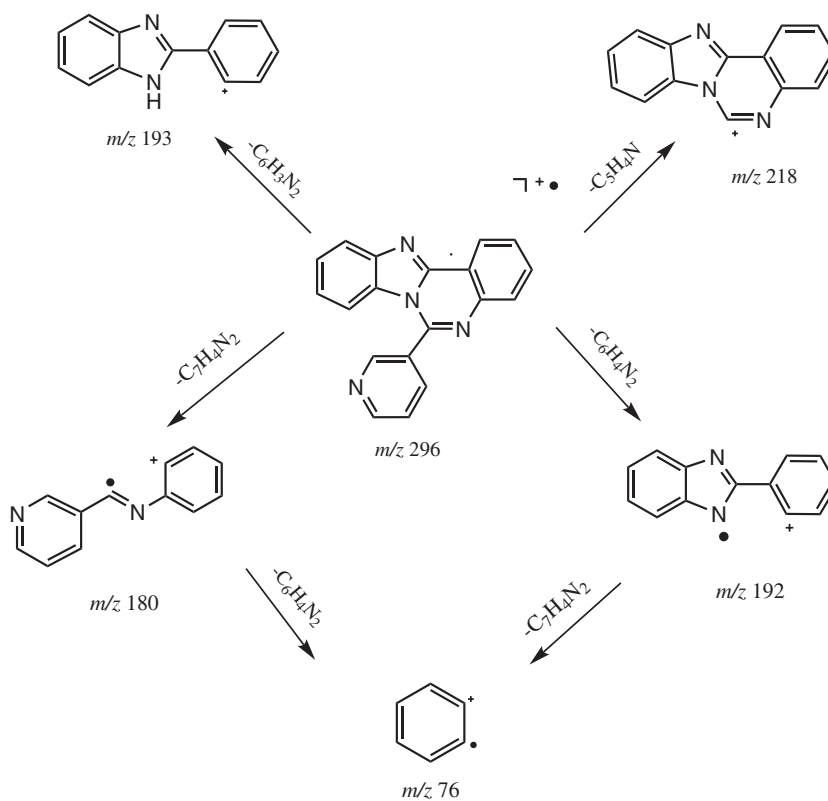


Figure S3. FAB mass spectrum of 6-(3-pyridyl)benzo[4,5]imidazo[1,2-c]quinazoline (**20**).



Scheme S1. FAB mass fragmentation pattern of 6-(3-pyridyl)benzo[4,5]imidazo[1,2-c]quinazoline (**20**).