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Article

Synthesis of Some New Mono, Bis-Indolo[1, 2-c]quinazolines: Evaluation of their Antimicrobial Studies

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Uma estratégia conveniente em três etapas é proposta para a síntese de mono e bis-indolo[1,2-c] quinazolinas, a partir de 2-(2-aminofenil)indol e aril aldeídos. Os novos compostos sintetizados foram caracterizados por análise elementar, IV, ^{1}H RMN, ^{13}C RMN, e espectrometria de massa. Todos os derivados foram testados para avaliação das suas atividades antibacterial (*S. aureus, B. subtilis, S. pyogenes, S. typhimurium, E. coli, K. pneumonia*) e antifúngica (*A. niger, C. albicans, T. viridae*) usando o método cup plate. Dentre os compostos testados, as mono- indolo[1,2-c] quinazolinas (**15-18**) exibiram boas atividades antibacteriais, enquanto **15** e **18** também mostraram notável atividade antifúngica. Especialmente, **19** e **20** exibiram forte atividade antibacteriana e antifúngica contra todas as cepas testadas.

A convenient three-step strategy is proposed for the synthesis of mono and bis-indolo[1,2-c] quinazolines from 2-(2-aminophenyl)indole and various aryl aldehydes. The newly synthesized compounds were characterized by elemental analysis, IR, ^{1}H NMR, ^{13}C NMR, and mass spectroscopic investigation. All the derivatives were screened for antibacterial (*S. aureus, B. subtilis, S. pyogenes, S. typhimurium, E. coli, K. pneumonia*) and antifungal (*A. niger, C. albicans, T. viridae*) activities by cup plate method. Among the compounds tested, mono- indolo[1,2-c] quinazolines (**15**-**18**) exhibited good antibacterial activities while **15** and **18** also showed notable antifungal activity. Especially, **19** and **20** exhibited stronger antibacterial as well as antifungal activity against all tested strains.

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

Introduction

The indole is a crucial heterocyclic skeleton often associated with pharmacological properties.[1,2] It is a fundamental constituent of a number of natural and synthetic products with biological activity.[3,4] Due to the structural similarity of indole nuclei with some naturally occurring compounds such as serotonin, tryptamine, hinckdentine A, they can easily interact with biomolecules of the living systems.[5,6] Heterocycles bearing an indole moiety are reported to show a broad spectrum of pharmacological and medicinal properties such as anti-inflammatory,[7,8] anticonvulsant,[9] antimicrobial,[10,11] antimalarial,[12,13] anticancer[14,15] and many other activities. The introduction of an additional substituent on the indole nuclei has been increasing attention in the expectation that such changes could potentially affect the interaction of the molecules with biological targets. Fused cyclic indole derivatives, such as indolocarbazoles,[16,17] indolo[2,3-b] quinolines,[18,19] indolo[l,2-c] quinazolines,[20,21] bis-indoles[22,23] and many others, have also interesting pharmacological properties. Moreover, indoles and their cyclic derivatives constitute an important class of compounds for new drug development in order to discover an effective compound against multi-drug-resistant microbial infections. Recently, Gurkok *et al.*[24] synthesized a series of indole-3-aldehyde and 5-bromoindole-3-aldehyde hydrazide and hydrazones and evaluated for their *in vitro* antimicrobial activities using the 2-fold serial dilution technique. Very recently, a series of 2-o-arylidineaminophenylindoles and their

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cyclic derivatives were synthesized and evaluated for their antibacterial as well as antifungal activities.[25] These observations have encouraged us to synthesize some new products containing the indole moiety hoping to obtain new compounds with potential biological activity. At last, we have succeeded in the preparation of several new indolo[1,2-c]quinazolines derivatives, which are structurally related to terrestrial or marine alkaloids (e.g. hinckdentine A). In addition all the newly synthesized quinazolines were screened for their *in vitro* antimicrobial activity.

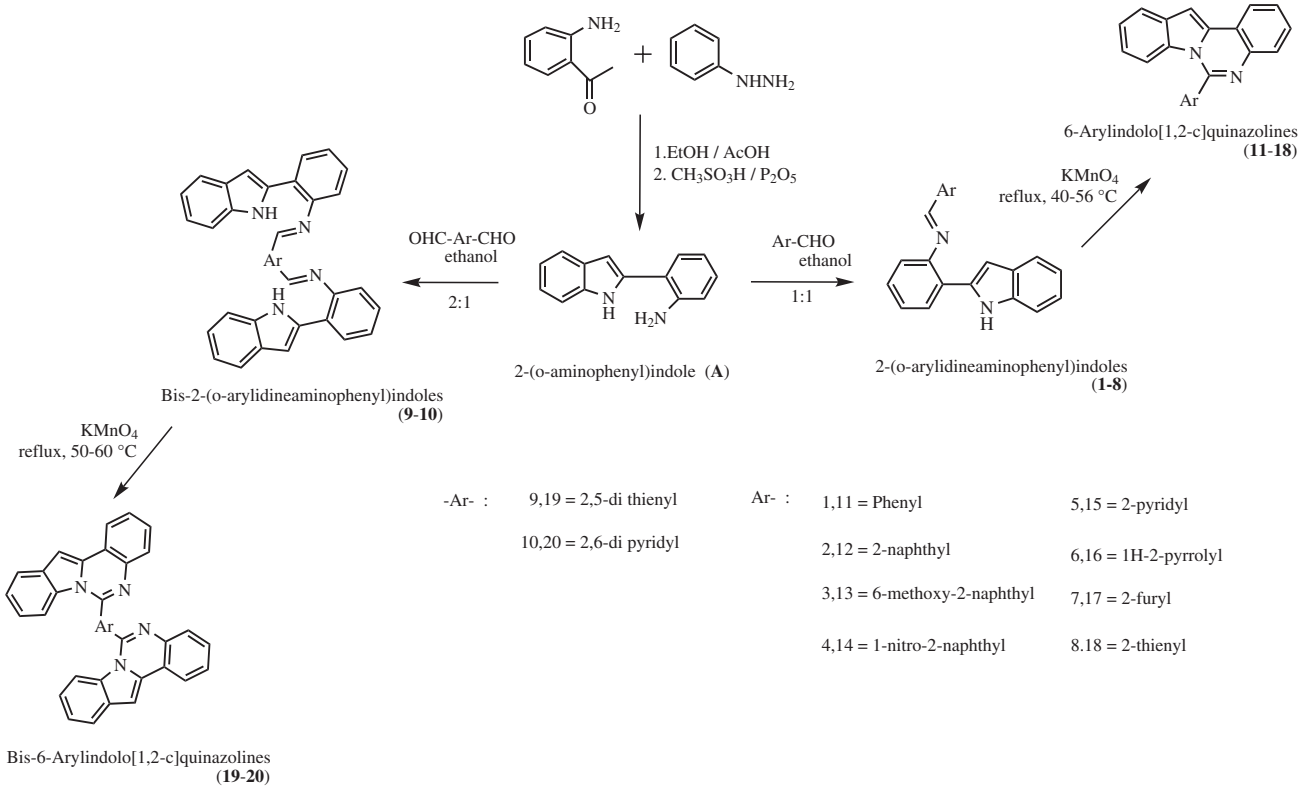
Results and Discussion

Chemistry

The indolo[1,2-*c*]quinazoline ring system was first prepared in 1956 by Kiang *et al.*,[26] and Cava and Billimoria[27] have reviewed the chemistry of indoloquinazolines, which are uncommon in nature. Moreover, they have published an interesting approach to the synthesis of hinckdentine A and other indolo[1,2-c]quinazoline derivatives.[5] Frere *et al.*[28] have developed a successful microwave assisted strategy for the synthesis of novel 6-substituted indolo[1,2-c] quinazolines by the condensation of 2-(2-aminophenyl) indole with 2-cyanobenzothiazoles. Molina *et al.*[29] reported the synthesis of indolo[1,2-c] quinazolines *via* iminophosphoranes.

In the present investigation, a convenient three-step strategy has been developed for the synthesis of mono and bis-indolo[1,2-c]quinazolines using 2-(2-aminophenyl) indole (**A**) as a key compound (Scheme 1). The required starting material **A** was prepared by the Fischer indole synthesis from phenylhydrazine hydrochloride and 2-amino acetophenone using a mixture of methane sulfonic acid and phosphorus pentoxide.[5] The condensation of 2-(2-aminophenyl)indole (**A**) with different aromatic aldehydes (Ar-CHO/CHO-Ar-CHO), yielded mono and bis-2-(2-arylideneaminophenyl)indoles, which on treatment with powdered $KMnO_4$ in acetone furnished mono and bis-indolo[1,2-c]quinazolines in good yields. The structural assignments to the new compounds were based on their elemental analysis and spectral (IR, ^{1}H NMR, ^{13}C NMR and mass) data.

The IR spectrum of 2-(2-aminophenyl)indole (**A**) exhibited an absorption band at 3380-3440 cm^{-1} due to the amino phenyl ring. All 2-(2-arylideneaminophenyl)indole intermediates (**1**-**10**) and precursor **A** exhibit characteristic IR absorption bands in the regions 3330-3400cm^{-1} and 1540-1560cm^{-1} indicative of –NH stretching and bending vibrations of indole ring, respectively.[30] The formation of intermediate azomethines (**1**-**10**) was identified by



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

disappearance of peaks at 1680-1695 cm^{-1} for –CHO and 3380-3440 cm^{-1} for $–NH_2$ of starting materials and at the same time appearance of band at 1610-1635 cm^{-1} which is characteristic for –CH=N group.[31] The formation of title compounds (**11**-**20**) were confirmed by the disappearance of the absorption maxima at 3330-3400 cm^{-1}, which are ascribed to the vibrations of NH group of the indole ring; at the same time the appearance of a new maximum at 1360-1380 cm^{-1}, which is characteristic for indolo[1,2-c] quinazoline ring with a tertiary nitrogen atom, appears.[32]

The exhibited chemical shifts obtained from ^{1}H NMR spectra of compounds **1**-**20** supported the proposed structures of the compounds.^{1}H NMR of **A** showed a singlet at δ 6.4 ppm, characteristic for $–NH_2$ group of amino phenyl ring and other singlet at δ 8.48 ppm, characteristic for –NH group of indolyl ring.[16] The condensation between **A** and aldehydes (**a**-**j**) was confirmed by the disappearance of signals at δ 6.4 corresponding to NH_2 protons of compound **A** and appearance of signals at δ 8.16-8.29 which is due to CH=N protons. Finally, in the title compounds disappearance of signals corresponding to –NH of indolyl ring and CH=N protons supports the indoloquinazoline ring structure.[32]

Further, ^{13}C NMR spectra showed confirmatory signals of the C=N carbon atoms and the aromatic carbons in the range of 148.9-167.9 ppm and 110.7-157.9 ppm respectively.[33]

The structures of all intermediates and title compounds were further confirmed by mass spectral analysis. ESI-MS spectra of all the compounds showed a single peak suggesting the molecular formulae. In addition, the FAB mass spectrum of compound (**11**) shows a parent peak at *m/z* (M+) 294 (100%), which confirms the proposed formula $C_{21}H_{14}N_2$. The major fragments were observed at *m/z* values of 217 (34.5%), 192 (65.2%), 191 (85.5%), 179 (48.2%), 77 (12.5%) and 76 (22.8%) which indicate the fragmentation pattern of compound **11**.

Biological study

Antimicrobial activity

All the newly synthesized quinazolines were evaluated for their *in vitro* antimicrobial activity against *S. aureus*, *B. subtilis*, *S. pyogenes* (Gram positive), *S. typhimurium, E. coli, K. pneumonia* (Gram negative) bacterial strains and *A.niger, C. albicans, T. viridae* fungal strains by cup plate method.[34-36] Ampicillin and Ketoconazole were used as standard drugs for bacteria and fungi respectively. Preliminary screening of quinazolines and standard drugs were performed at fixed concentrations of 1000 μg mL^{-1}. Inhibition was recorded by measuring the diameter of the inhibition zone at the end of 24 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. The antimicrobial screening revealed that some of the compounds (**15**-**20**) showed high activity against all bacterial and fungal strains. In particular, bis-indolo[1,2-c] quinazolines (**19** and **20**) showed excellent activity against all tested strains.

Determination of minimum inhibitory concentration (MIC)

The minimum inhibitory concentration of potent compounds (**15**-**20**) against all bacterial and fungal strains was determined by liquid dilution method.[34-36] Stock solutions of tested compounds with 2.5, 5, 10, 15, 20, 25, 30, 35, 40, 45 and 50 μg 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 inoculums 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 drugs Ampicillin and Ketoconazole for comparison. The minimum inhibitory concentration at which no growth was observed was taken as the MIC values (Table 2). The comparison of the MICs (in μg mL^{-1}) of potent compounds and standard drugs against tested strains are presented in Figure 1. It was found that **15**-**18** compounds have highest activity against all bacterial and fungal strains with MIC value (2.5-15 μg mL^{-1}). Furthermore, bis-indolo[1,2-c] quinazolines (**19** and **20**) exhibited potent inhibitory activity (MIC range 2.5-5 μg mL^{-1}) against all the bacterial and fungal strains even than standard drugs Ampicillin and Ketoconazole.

Conclusions

In this report, easy and useful method to obtain biologically active mono and bis-6-substituted indolo[1,2-c]quinazoline derivatives have been presented and all the synthesized compounds were screened for their antimicrobial activity against different bacterial and fungal strains. From the antimicrobial data it seems that compounds which contain two quinazoline moieties in their structures (**19** and **20**) and heterocyclic moiety at C_6 position (**15**-**20**) seem to be more potent even than standard drugs ampicillin and ketoconazole.

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

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

[a]Ampicillin; [b]Ketoconazole.

Table 2. MIC values of potent 6-arylindolo[1,2-c]quinazolines (**15**-**20**) and standard drugs

Compound	MIC / (μg mL^{-1})								
	Gram-positive bacteria			Gram-negative bacteria			Fungi		
	S. aureus	*B. subtilis*	*S. pyogenes*	*S. typhimurium*	*E. coli*	*K. pneumonia*	*A. niger*	*C. albicans*	*T. viridae*
15	10	2.5	10	10	5	2.5	10	15	15
16	2.5	10	15	5	10	5	10	5	5
17	5	10	2.5	10	15	5	2.5	15	10
18	5	2.5	5	5	5	5	5	5	5
19	2.5	2.5	2.5	2.5	2.5	2.5	2.5	5	2.5
20	2.5	5	5	2.5	5	2.5	5	2.5	5
Std	10[a]	20[a]	25[a]	10[a]	15[a]	10[a]	15[b]	25[b]	20[b]

[a]Ampicillin; [b]Ketoconazole.

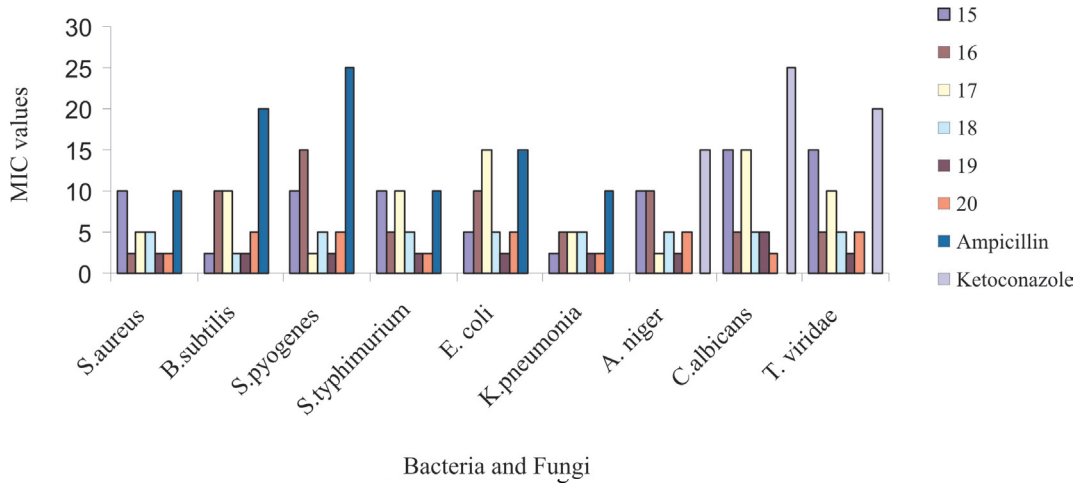


Figure 1. Comparison of MIC values (in μg mL^{-1}) of quinazolines and standard drugs against different bacteria and fungi.

Experimental

All solvents used were of analytical grade. TLC analysis was done using precoated silica gel plates and visualization was done using 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. ^{1}H NMR spectra were acquired at 400 MHz, and ^{13}C NMR at 67.93 MHz on a Bruker NMR spectrometer (Bruker Bioscience,

USA). FAB mass spectra were recorded on a Finnigan-MAT 1020 instrument (Thermo Electron Corporation, Bremen, Germany). An ion trap mass spectrometer (Agilent Series LC/MSD Trap SL) equipped with an electrospray ionization (ESI) source was used for MS analyses (Agilent, Palo Alto, CA, USA). Microorganisms like *Staphylococcus aureus* (ATCC 25923), *Bacillus subtilis* (ATCC 9372), *Streptococcus pyogenes* (ATCC 19615) (Gram positive) and *Salmonella typhimurium* (ATCC 14028)*, Escherichia coli* (ATCC *25922), Klebsiella pneumonia* (ATCC *3882)* (Gram negative) bacterial strains and *Aspergillus niger* (ATCC 16404), *Candida albicans* (ATCC 10231) and *Trichoderma viridae* (IAM 5061) fungal strains were used in the present investigation.

*Preparation of 2-(2-aminophenyl)indzole (**A**)*

The precursor 2-(2-aminophenyl)indole (**A**) was obtained by the Fischer indole synthesis from phenylhydrazine hydrochloride and 2-amino acetophenone using a mixture of methane sulfonic acid and phosphorus pentoxide at 85 °C. All the reactions were carried out according to the procedure described by Billimoria and Cava.[5]

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

To a solution of precursor 2-(2-aminophenyl)indole (**A**, 0.416 g, 2 mmol for **1**-**8** and 0.832 g, 4 mmol for **9**-**10**) in 20-40 mL of ethanol, 2 mmol of Ar-CHO/ CHO-Ar-CHO and few drops of acetic acid was added with vigorous stirring. The reaction mixture was then refluxed for 3 h. After cooling, the deposited solid product was collected by filtration and recrystalized from an ethanol/ dichloromethane-methanol mixture.

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

The final compounds mono, bis-indolo[1,2-c] quinazolines (**11**-**20**) were prepared from intermediate azomethines (**1**-**10)** through oxidative cyclisation method. Powdered potassium permanganate (1.5 equiv.) was added to a solution of the azomethyne compound (**11**-**20**) in 50-75 mL of acetone. The reaction mixture was refluxed under heat (40-60 °C) for 30 min. It was then filtered hot, and an equal volume of hot water added to the filtrate. The final products, 6-substituted indolo[1,2-c]quinazolines (**11**-**20**) rapidly separated, and was collected by filtration and recrystalized from dimethylformamide/ethanol.

*N-benzylidene-2-(1H-indol-2-yl)benzenamine (**1**)*

Yield 78%; mp 196-198 °C; IR (KBr) ν_{max}/cm^{-1}: 3400, 1650, 1595, 1570, 1128; ^{1}H NMR (400 MHz, $CDCl_3$) δ in ppm 6.73 (s, 1H, Ar), 6.95-7.18 (m, 3H, Ar), 7.23-7.65 (m, 10H, Ar), 8.10 (s, 1H, CH=N), 8.29 (s, 1H, -NH); ^{13}C NMR (67.93 MHz, $CDCl_3$) δ 114.4, 118.6, 121.5, 123.6, 126.7, 130.2, 131.5, 132.4, 136.2, 140.1, 142.5, 143.6, 146.5, 165.3 (21C, Ar-C); Anal. Found: C, 85.15; H, 5.51; N, 9.46%. Calc. for $C_{21}H_{16}N_2$: C, 85.11; H, 5.44; N, 9.45%. MS: $[M]^+$ at *m/z* 296.

*2-(1H-indol-2-yl)-N-(naphthalen-2-ylmethylene) benzenamine (**2**)*

Yield 75%; mp 222-224 °C; IR (KBr) ν_{max}/cm^{-1}: 3398, 1641, 1605, 1575, 1130; ^{1}H NMR (400 MHz, $CDCl_3$) δ in ppm 6.71 (s, 1H, Ar), 6.90-7.11 (m, 2H, Ar), 7.25 -7.64 (m, 9H, Ar), 7.75 -7.94 (m, 4H, Ar), 8.16 (s, 1H, CH=N), 8.35 (s, 1H, –NH); ^{13}C NMR (67.93 MHz, $CDCl_3$) δ 113.9, 117.9, 121.5, 123.2, 126.6, 130.2, 131.9, 132.5, 135.3, 140.8, 142,2, 145.6, 148.5, 164.9 (25C, Ar-C); Anal. Found: C, 86.70; H, 5.22; N, 8.13%. Calc. for $C_{25}H_{18}N_2$: C, 86.68; H, 5.24; N, 8.09%. MS: $[M]^+$ at *m/z* 346.

*2-(1H-indol-2-yl)-N-((6-methoxynaphthalen-2-yl) methylene)benzenamine (**3**)*

Yield 79%; mp 201-203 °C; IR (KBr) ν_{max}/cm^{-1}: 3405, 1637, 1605, 1588, 1130, 1038, 850; ^{1}H NMR (400 MHz, $CDCl_3$) δ in ppm 3.90 (s, 3H, OCH3), 6.72 (s, 1H, Ar), 6.92-7.10 (m, 3H, Ar), 7.25-7.60(m, 9H, Ar), 7.73-7.82 (m, 2H, Ar), 8.15 (s, 1H, CH=N), 8.29 (s, 1H, –NH); ^{13}C NMR (67.93 MHz, $CDCl_3$) δ 56.2, (1C, –OCH_3), 113.8, 119.5, 120.7, 123.6, 127.1, 130.2, 131.5, 132.3, 141.7, 142,2, 147.5, 151.5, 153.7, 166.9 (25C, Ar-C); Anal. Found: C, 83.01; H, 5.38; N, 7.43%. Calc. for $C_{26}H_{20}N_2O$: C, 82.95; H, 5.35; N, 7.44%. MS: $[M]^+$ at *m/z* 376.

*2-(1H-indol-2-yl)-N-((1-nitronaphthalen-2-yl)methylene) benzenamine (**4**)*

Yield 81%; mp 231-233 °C; IR (KBr) ν_{max}/cm^{-1}: 3395, 1638, 1608, 1589, 1524, 1346, 1126, 850; ^{1}H NMR (400 MHz, $CDCl_3$) δ in ppm 6.71 (s, 1H, Ar), 6.90-7.12 (m, 2H, Ar), 7.25-7.68(m, 8H, Ar), 7.93-8.02 (m, 2H, Ar), 8.16 (s, 1H, CH=N), 8.23-8.25 (m, 2H, Ar), 8.59 (s, 1H, –NH); ^{13}C NMR (67.93 MHz, $CDCl_3$) δ 114.2, 117.5, 119.0, 122.5, 125.2, 126.8, 132.3, 136.8, 142.1, 143.6, 147.8, 154.1, 167.2 (25C, Ar-C); Anal. Found: C, 76.80; H, 4.56; N, 10.78%. Calc. for $C_{25}H_{17}N_3O_2$: C, 76.71; H, 4.38; N, 10.74%. MS: $[M]^+$ at *m/z* 391.

*2-(1H-indol-2-yl)-N-(pyridin-2-ylmethylene) benzenamine (**5**)*

Yield 78%; mp 185-187 °C; IR (KBr) ν_{max}/cm^{-1}: 3400, 1628, 1605, 1585, 1109; ^{1}H NMR (400 MHz, $CDCl_3$) δ in

ppm 6.74 (s, 1H, Ar), 6.92-7.11 (m, 3H, Ar), 7.28-7.65 (m, 8H, Ar), 8.18 (s, 1H, CH=N), 8.32 (s, 1H, –NH), 8.58 (m, 1H, Ar); ^{13}C NMR (67.93 MHz, $CDCl_3$) δ 114.3, 118.1, 122.5, 123.6, 126.5, 130.5, 131.7, 132.9, 136.2, 141.5, 142,3, 143.4, 146.7, 148.1, 155.8, 165.9 (20C, Ar-C); Anal. Found: C, 80.87; H, 5.09; N, 14.15%. Calc. for $C_{20}H_{15}N_3$: C, 80.78; H, 5.08; N, 14.13%. MS: $[M]^+$ at *m/z* 297.

*N-((1H-pyrrol-2-yl)methylene)-2-(1H-indol-2-yl) benzenamine(**6**)*

Yield 75%; mp 205-207 °C; IR (KBr) ν_{max}/cm^{-1}: 3395, 3215, 1638, 1606, 1578, 1132; ^{1}H NMR (400 MHz, $CDCl_3$) δ in ppm 6.70 (s, 1H, Ar), 6.12-7.10 (m, 5H, Ar), 7.22-7.61 (m, 6H, Ar), 8.15 (s, 1H, CH=N), 8.56 (s, 1H, –NH), 8.85 (s, 1H, pyrrolyl NH); ^{13}C NMR (67.93 MHz, $CDCl_3$) δ 113.5, 114.2, 118.7, 120.9, 123.2, 126.6, 130.4, 131.7, 133.1, 136.7, 140.3, 141.6, 145.7, 146.2, 150.9 (19C, Ar-C); Anal. Found: C, 80.01; H, 5.35; N, 14.82%. Calc. for $C_{19}H_{15}N_3$: C, 79.98; H, 5.30; N, 14.73%. MS: $[M]^+$ at *m/z* 285.

*N-(furan-2-ylmethylene)-2-(1H-indol-2-yl)benzenamine (**7**)*

Yield 80%; mp 215-217 °C; IR (KBr) ν_{max}/cm^{-1}: 3398, 1636, 1608, 1583, 1130; ^{1}H NMR (400MHz, $CDCl_3$) δ in ppm 6.45 (s, 1H, Ar), 6.72 (s, 1H, Ar), 6.80-7.11 (m, 3H, Ar), 7.29-7.61 (m, 7H, Ar), 8.14 (s, 1H, CH=N), 8.28 (s, 1H, –NH); ^{13}C NMR (67.93 MHz, $CDCl_3$) δ 112.4, 113.9, 114.4, 120.8, 122.9, 123.4, 126.1, 130.7, 131.2, 132.5, 140.6, 142.8, 143.4, 146.2, 155.6 (19C, Ar-C); Anal. Found: C, 79.72; H, 4.99; N, 9.86%. Calc. for $C_{19}H_{14}N_2O$: C, 79.70; H, 4.93; N, 9.78%. MS: $[M]^+$ at *m/z* 286.

*2-(1H-indol-2-yl)-N-(thiophen-2-ylmethylene) benzenamine (**8**)*

Yield 76%; mp 221-223 °C; IR (KBr) ν_{max}/cm^{-1}: 3395, 1638, 1610, 1586, 1132, 698; ^{1}H NMR (400MHz,$CDCl_3$) δ in ppm 6.73 (s, 1H, Ar), 6.92-7.14 (m, 4H, Ar), 7.28-7.62 (m, 7H, Ar), 8.16 (s, 1H, CH=N), 8.29 (s, 1H, –NH); ^{13}C NMR (67.93 MHz, $CDCl_3$) δ 114.5, 118.8, 120.4, 123.2, 126.8, 130.2, 131.5, 132.8, 133.3, 140.2, 143.6, 146.4, 147.8, 148.9 (19C, Ar-C); Anal. Found: C, 75.52; H, 4.69; N, 9.28%. Calc. for $C_{19}H_{14}N_2S$: C, 75.47; H, 4.67; N, 9.26%. MS: $[M]^+$ at *m/z* 302.

*N-((5-((2-(1H-indol-2-yl)phenylimino)methyl)thiophen-2-yl)methylene)-2-(1H-indol-2-yl)benzenamine (**9**)*

Yield 78%; mp 245-247 °C; IR (KBr) ν_{max}/cm^{-1}: 3400, 1625, 1602, 1586, 1128, 696; ^{1}H NMR (400 MHz, $CDCl_3$) δ in ppm 6.74 (s, 2H, Ar), 6.91-7.12 (m, 4H, Ar), 7.21 (s, 2H, Ar), 7.31-7.62 (m, 12H, Ar), 8.14 (s, 2H, CH=N), 8.32 (s, 2H, –NH); ^{13}C NMR (67.93 MHz, $CDCl_3$) δ 113.8, 114.2, 120.3, 123.5, 125.6, 127.1, 128.9, 130.2, 131.6, 132.8, 140.9, 142.6, 144.3, 145.7, 146.2, 146.9, 152.4 (34C, Ar-C); Anal. Found: C, 78.46; H, 4.72; N, 10.78%. Calc. for $C_{34}H_{24}N_4S$: C, 78.44; H, 4.65; N, 10.76%. MS: $[M]^+$ at *m/z* 520.

*N-((6-((2-(1H-indol-2-yl)phenylimino)methyl)pyridin-2-yl) methylene)-2-(1H-indol-2-yl)benzenamine (**10**)*

Yield 78%; mp 238-240 °C; IR (KBr) ν_{max}/cm^{-1}: 3405, 1645, 1610, 1585, 1132; ^{1}H NMR (400 MHz, $CDCl_3$) δ in ppm 6.72 (s, 2H, Ar), 6.90-7.11 (m, 4H, Ar), 7.21-7.62 (m, 14H, Ar), 7.82 (m, 1H, Ar), 8.16 (s, 2H, CH=N), 8.38 (s, 2H, –NH); ^{13}C NMR (67.93 MHz, $CDCl_3$) δ 114.4, 114.7, 121.8, 123.2, 125.7, 127.9, 128.1,130.6, 131.3, 132.7, 141.3, 142.3, 144.8, 145.8, 146.1, 155.5, 167.9 (35 C, Ar-C) Anal. Found: C, 81.57; H, 4.92; N, 13.63%. Calc. for $C_{35}H_{25}N_5$: C, 81.53; H, 4.89; N, 13.58%. MS: $[M]^+$ at *m/z* 515.

*6-phenylindolo[1,2-c]quinazoline (**11**)*

Yield 81%; mp 210-212 °C; IR (KBr) ν_{max}/cm^{-1}: 1620, 1581, 1535, 1457, 1378, 775, 741, 733; ^{1}H NMR (400 MHz, DMSO-d_6) δ in ppm 7.01-7.12 (m, 3H, Ar), 7.25-7.51 (m, 4H, Ar), 7.61-7.88 (m, 7H, Ar); ^{13}C NMR (67.93 MHz, DMSO-d_6) δ 113.2, 119.1, 120.2, 122.7, 124.4, 126.3, 127.9, 129.1, 130.5, 131.2, 132.4, 133.8, 145.4, 146.5, 152.8 (21 C, Ar-C); Anal. Found: C, 85.73; H, 4.80; N, 9.56%. Calc. for $C_{21}H_{14}N_2$: C, 85.69; H, 4.79; N, 9.52%. MS: $[M]^+$ at *m/z* 294.

*6-(2-naphthyl)indolo[1,2-c]quinazoline (**12**)*

Yield 80%; mp 235-237 °C; IR (KBr) ν_{max}/cm^{-1}: 1625, 1585, 1530, 1459, 1385, 773, 741, 732; ^{1}H NMR (400 MHz, DMSO-d_6) δ in ppm 7.02 (m, 1H, Ar), 7.21-7.56 (m, 6H, Ar), 7.61-7.72 (m, 3H, Ar), 7.80-8.03 (m, 5H, Ar), 8.32 (s, 1H, Ar); ^{13}C NMR (67.93 MHz, DMSO-d_6) δ 112.3, 120.3, 121.4, 122.2, 123.9, 125.6, 129.1, 130.3, 132.5, 141.4, 145.5, 151.2, 156.4, 164.3 (25 C, Ar-C); Anal. Found: C, 87.20; H, 4.71; N, 8.15%. Calc. for $C_{25}H_{16}N_2$: C, 87.18; H, 4.68; N, 8.13%. MS: $[M]^+$ at *m/z* 344.

*6-(6-methoxy-2-naphthyl)indolo[1,2-c]quinazoline (**13**)*

Yield 78%; mp 218-220 °C; IR (KBr) ν_{max}/cm^{-1}: 1628, 1585, 1540, 1458, 1375, 1042, 775, 743, 731; ^{1}H NMR (400 MHz, DMSO-d_6) δ in ppm 3.90 (s, 3H, OCH3), 7.01-7.06 (m, 2H, Ar), 7.25-7.52 (m, 5H, Ar), 7.60-8.13 (m, 7H, Ar), 8.36 (s, 1H, Ar); ^{13}C NMR (67.93 MHz, DMSO-d_6) δ 56.4, (1C, –OCH3), 113.2, 119.8, 121.2, 122.3, 124.2, 125.8, 129.3, 130.4, 131.7, 132.6, 142.1, 145.3, 150.2, 155.9, 164.9 (25C, Ar-C); Anal. Found: C, 83.42; H, 4.89; N, 7.50%. Calc. for $C_{26}H_{18}N_2O$: C, 83.40; H, 4.85; N, 7.48%. MS: $[M]^+$ at *m/z* 374.

*6-(1-nitro-2-naphthyl)indolo[1,2-c]quinazoline (**14**)*

Yield 78%; mp 225-227 °C; IR (KBr) ν_{max}/cm^{-1}: 1635, 1585, 1528, 1460, 1386, 852, 775, 741, 733; ^{1}H NMR (400 MHz, DMSO-d$_6$) δ in ppm 7.04 (m, 1H, Ar), 7.28-7.42 (m, 3H, Ar), 7.58-7.73 (m, 5H, Ar), 7.85-8.12 (m, 4H, Ar), 8.28-8.40 (m, 2H, Ar); ^{13}C NMR (67.93 MHz, DMSO-d_6) δ 112.6, 119.7, 121.2, 123.5, 124.2, 125.5, 129.7, 130.3, 131.8, 141.9, 145.8, 152.4, 164.8 (25 C, Ar-C); Anal. Found: C, 77.15; H, 3.90; N, 10.80%. Calc. for $C_{25}H_{15}N_3O_2$: C, 77.11; H, 3.88; N, 10.79%. MS: [M]$^+$ at *m/z* 389.

*6-(2-pyridyl)indolo[1,2-c]quinazoline (**15**)*

Yield 76%; mp 209-211°C; IR (KBr) ν_{max}/cm^{-1}: 1625, 1608, 1535, 1448, 1380, 773, 740, 733; ^{1}H NMR (400 MHz, DMSO-d$_6$) δ in ppm 7.02-7.05 (m, 2H, Ar), 7.21-7.72 (m, 8H, Ar), 7.82-7.86 (m, 2H, Ar), 8.69 (m, 1H, Ar); ^{13}C NMR (67.93 MHz, DMSO-d_6) δ 113.1, 120.2, 121.5, 122.9, 125.1, 126.5, 129.2, 130.6, 131.8, 133.2, 138.5, 142.3, 145.7, 146.2, 151.3, 153.5, 154.2 (20 C, Ar-C); Anal. Found: C, 81.37; H, 4.48; N, 14.24%. Calc. for $C_{20}H_{13}N_3$: C, 81.34; H, 4.44; N, 14.23%. MS: [M]$^+$ at *m/z* 295.

*6-(1H-2-pyrrolyl)indolo[1,2-c]quinazoline (**16**)*

Yield 79%; mp 193-195 °C; IR (KBr) ν_{max}/cm^{-1}: 3215, 1638, 1610, 1581, 1469, 1388, 772, 743, 736; ^{1}H NMR (400 MHz, DMSO-d$_6$) δ in ppm 5.62 (m, 1H, Ar), 6.35 (m, 1H, Ar), 7.01-7.05 (m, 2H, Ar), 7.23-7.85 (m, 8H, Ar), 10.6 (s, 1H, pyrrolyl NH);; ^{13}C NMR (67.93 MHz, DMSO-d_6) δ 112.6, 113.9, 119.5, 120.7, 122.5, 124.5, 125.3, 127.1, 129.6, 130.4, 132.4, 141.7, 143.4, 145.3, 146.2, 148.3, 150.1 (19C, Ar-C); Anal. Found: C, 80.56; H, 4.68; N, 14.85%. Calc. for $C_{19}H_{13}N_3$: C, 80.54; H, 4.62; N, 14.83%. MS: [M]$^+$ at *m/z* 283.

*6-(2-furyl)indolo[1,2-c]quinazoline (**17**)*

Yield 75%; mp 224-226 °C; IR (KBr) ν_{max}/cm^{-1}: 1640, 1608, 1579, 1470, 1388, 771, 742, 736; ^{1}H NMR (400 MHz, DMSO-d$_6$) δ in ppm 6.25-6.43 (m, 2H, Ar), 7.04 (m, 1H, Ar), 7.25-7.83 (m, 9H, Ar); ^{13}C NMR (67.93 MHz, DMSO-d_6) δ 112.2, 113.5, 120.8, 121.3, 122.9, 124.4, 126.5, 126.9, 130.5, 131.3, 132.5, 138.1, 142.9, 145.4, 146.5, 147.7, 149.5 (19C, Ar-C); Anal. Found: C, 80.30; H, 4.29; N, 9.86%. Calc. for $C_{19}H_{12}N_2O$: C, 80.27; H, 4.25; N, 9.85%. MS: [M]$^+$ at *m/z* 284.

*6-(2-thienyl)indolo[1,2-c]quinazoline (**18**)*

Yield 76%; mp 236-238 °C; IR (KBr) ν_{max}/cm^{-1}: 1638, 1609, 1582, 1465, 1388, 772, 743, 748, 692; ^{1}H NMR (400 MHz, DMSO-d_6) δ in ppm 6.45 (s, 1H, Ar), 7.01-7.05 (m, 2H, Ar), 7.28-7.85 (m, 9H, Ar); ^{13}C NMR (67.93 MHz, DMSO-d_6) δ 112.2, 119.5, 120.8, 121.5, 123.2, 124.1, 125.5, 126.4, 130.3, 131.7, 132.7, 136.9, 142.7, 145.4, 146.7, 148.2, 149.7 (19C, Ar-C); Anal. Found: C, 76.01; H, 4.02; N, 9.35%. Calc. for $C_{19}H_{12}N_2S$: C, 75.97; H, 4.03; N, 9.33%. MS: [M]$^+$ at *m/z* 300.

*6-(5-indolo[1,2-c]quinazolin-6-yl-2-thienyl)indolo[1,2-c] quinazoline (**19**)*

Yield 79%; mp 250-252 °C; IR (KBr) ν_{max}/cm^{-1}: 1640, 1605, 1458, 1382, 1135, 774, 740, 732, 695; ^{1}H NMR (400 MHz, DMSO-d_6) δ in ppm 6.68 (s, 2H, Ar), 7.02-7.07 (m, 2H, Ar), 7.25-7.86 (m, 16H, Ar); ^{13}C NMR (67.93 MHz, DMSO-d_6) δ 110.7, 111.4, 112.6, 119.2, 120.5, 121.8, 122.8, 123.8, 126.4, 129.2, 130.6, 132.3, 133.7, 138.4, 140.7, 143.4, 145.6, 147.8, 150.2, 152.8 (34C, Ar-C); Anal. Found: C, 79.06; H, 3.98; N, 10.85%. Calc. for $C_{34}H_{20}N_4S$: C, 79.05; H, 3.90; N, 10.84%. MS: [M]$^+$ at *m/z* 516.

*6-(6-indolo[1,2-c]quinazolin-6-yl-2-pyridyl)indolo[1,2-c] quinazoline (**20**)*

Yield 72%; mp 255-256 °C; IR (KBr) ν_{max}/cm^{-1}: 1628, 1606, 1586, 1385, 1128, 745, 736, 730; ^{1}H NMR (400 MHz, DMSO-d_6) δ in ppm 7.02-7.07 (m, 4H, Ar), 7.25-7.82 (m, 16H, Ar), 7.92 (t, 1H, Ar, *J* 7.8 Hz); ^{13}C NMR (67.93 MHz, DMSO-d$_6$) δ 112.6, 113.7, 120.8, 121.3, 122.4, 123.6, 124.6, 126.5, 128.2, 131.7, 133.4, 135.8, 139.2, 140.3, 143.9, 145.6, 148.2, 152.2, 153.7, 155.9 (35C, Ar-C); Anal. Found: C, 82.16; H, 4.16; N, 13.72%. Calc. for $C_{35}H_{21}N_5$: C, 82.17; H, 4.14; N, 13.69%. MS: [M]$^+$ at *m/z* 511.

Supplementary Information

Supplementary data are available free of charge at http://jbcs.sbq.org.br, as PDF file.

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