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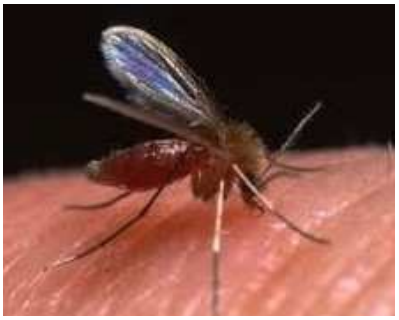
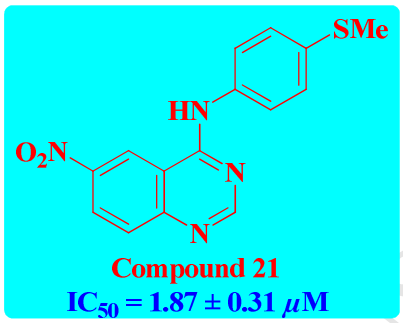
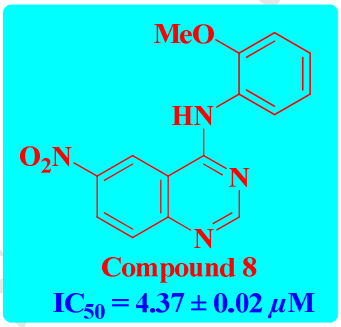
Syed Muhammad Saad,[1] Nida Ghouri,[1] Shahnaz Perveen,[2] Khalid Mohammed Khan,[1,*] M. Iqbal Choudhary[1,3]

[a]H. E. J. Research Institute of Chemistry, International Center for Chemical and Biological Sciences, University of Karachi, Karachi-75270, Pakistan
[b]PCSIR Laboratories Complex, Karachi, Shahrah-e-Dr. Salimuzzaman Siddiqui, Karachi-75280, Pakistan
[c]Department of Biochemistry, Faculty of Sciences, King Abdulaziz University, Jeddah-21412, Saudi Arabia





Compound 21
IC_{50} = 1.87 ± 0.31 μM



Compound 8
IC_{50} = 4.37 ± 0.02 μM

4-Arylamino-6-nitroquinazolines: Synthesis and their activities against neglected disease Leishmaniasis

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[1]*H. E. J. Research Institute of Chemistry, International Center for Chemical and Biological Sciences, University of Karachi, Karachi-75270, Pakistan*

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[3]*Department of Biochemistry, Faculty of Sciences, King Abdulaziz University, Jeddah-21412, Saudi Arabia*

Abstract

4-Arylamino-6-nitroquinazolines (**2-25**) were synthesized and evaluated for their leishmanicidal activities against *Leishmania major* promastigotes *in vitro* with IC_{50} values = 1.87-61.48 μM. Among the twenty four synthetic derivatives, 4-[4′-(methylsulfanyl)phenyl]amino-6-nitroquinazoline (**21**), and 4-(2′-methoxyphenyl)amino-6-nitroquinazoline (**8**) showed excellent antileishmanial activities with IC_{50} values 1.87 ± 0.31 and 4.37 ± 0.02 μM, respectively, more active than the standard drug, pentamidine (IC_{50} = 5.09 ± 0.09 μM). Compound **16** (IC_{50} = 6.53 ± 0.21 μM) displayed an activity comparable to the standard. Compounds **15** (IC_{50} = 9.04 ± 0.03 μM), **18** (IC_{50} = 12.28 ± 0.18 μM), **14** (IC_{50} = 19.87 ± 0.22 μM), and **5** (IC_{50} = 24.03 ± 2.71 μM) also showed good activities.

Keywords

4-Arylamino-6-nitroquinazolines; *Leishmania major*; Antileishmanial Agents.

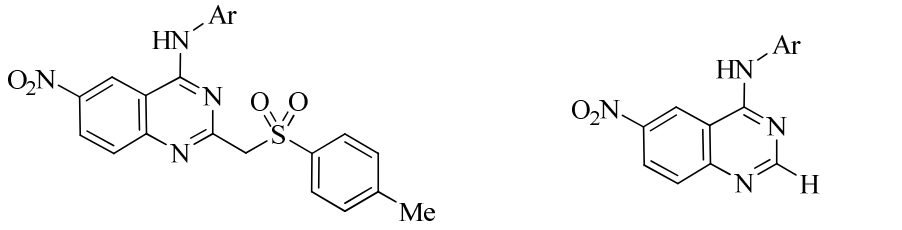
*Corresponding Author: khalid.khan@iccs.edu, hassaan2@super.net.pk, Tel.: 0092-21-34824910; Fax: 0092-21-34819018

1. Introduction

Leishmaniasis is a vector-borne disease, caused by the bite of different species of phlebotomine sandflies, which release protozoa of the genus *Leishmania* parasites [1]. Among all tropical diseases, leishmaniasis is ranked fourth in morbidity, and second in mortality rates [2]. Leishmaniasis is widespread among 88 countries of the world, with the exception of Antarctica [3]. It has affected 12 million people and to make the case worst, this figure increases to 2 million every year [4,5]. Based on types of species and response of host immune, leishmaniasis has three basic clinical forms; cutaneous, mucosal, and visceral leishmaniases. Cutaneous leishmaniasis (CL) is the most common type. It is mainly caused by *L. braziliensis*, *L. major*, *L. mexicana*, *L. tropica*, and several other species [6]. Mucosal leishmaniasis (ML) is usually caused by *L. braziliensis*. Damage of the palate, nasal septum, and mucous membranes are associated with this disease [7,8]. Visceral leishmaniasis (VL) is usually caused by *L. infantum* and *L. donovani*. It is the most severe form of leishmaniasis which can cause death, if left untreated [9,10].

Treatment of leishmaniasis is based on synthetic drugs, such as fluconazole, amphotericin B, pentamidine, pentavalent antimonials, and miltefosine [11,12]. Treatment of leishmaniasis is associated with toxic effects, high cost, and emerging resistance [13,14]. Hence, it is a necessity to develop drugs which are effective, safe, and possessing no or minimum toxicity, to cure leishmaniasis.

Quinazolines are the nitrogenous binuclear compounds with antitubercular [15], antimicrobial [16], anti-inflammatory [17], anticonvulsant [18], antiallergic [19], antihyperlipidemic [20], and antiviral [21] properties. Many drugs possess quinazoline moiety as core part of their structures. This indicates the importance of quinazoline as a privileged pharmacophore [22-25]. Literature survey reveals some quinazoline derivatives possess leishmanicidal activities [26-29]. Our research group is focusing on the discovery of the antileishmanial lead molecules since last one decade [30-39]. Few years ago, antiparasitic studies were conducted on the analogs of substituted 4-arylamino-6-nitro-2-sulfonylatedquinazolines [40]. In the light of these studies, we synthesized structurally similar some easy to prepare analogs of 4-arylamino-6-nitroquinazolines **2**-**25** (Figure-1) and evaluated for their leishmanicidal effects (Table-1). Nine compounds **4**, **8**, **9**, **13**, **14**, and **21**-**24** are new, while remaining compounds are previously reported [41-44].



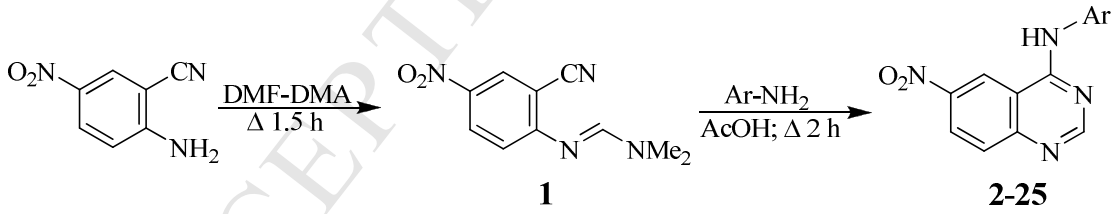
4-Arylamino-6-nitro-2-sulfonylatedquinazolines 4-Arylamino-6-nitroquinazolines

Figure-1: Structures of 4-arylamino-6-nitro-2-sulfonylatedquinazolines and 4-arylamino-6-nitroquinazolines.

2. Results and Discussion

2.1. Chemistry

For the study of antileishmanial activity, twenty-four derivatives of 4-arylamino-6-nitroquinazolines were synthesized by reacting (*E*)-*N'*-(2-cyano-4-nitrophenyl)-*N*,*N*-dimethylformimidamide (**1**) with various aniline derivatives in acetic acid under reflux conditions. Precipitates appeared when water was added into the reaction mixture. The precipitates were filtered, and dried under vacuum (Scheme-1). Prior to this, (*E*)-*N'*-(2-cyano-4-nitrophenyl)-*N*,*N*-dimethylformimidamide (**1**) was synthesized and analyzed by X-ray crystallography as our research group previously reported [45]. The chemical structures of these derivatives were inferred by ^{1}H-NMR, ^{13}C-NMR, EI-MS, and IR spectroscopy. All synthesized compounds yielded acceptable elemental analyses, and HREI-MS data.



1 **2-25**

Scheme-1: Synthesis of 4-arylamino-6-nitroquinazoline derivatives **2-25**.

2.1.1. Characteristic Spectral Feature of Representative Compound 21

^{1}H- and ^{13}C-NMR spectra of most potent anti-leishmanial compound **21** were recorded in deuterated DMSO. In ^{1}H-NMR spectrum (Figure-2), a downfield broad singlet signal appeared at δ_H 10.44 was due to the acidic NH proton. The lone pair of this nitrogen is involved in extensive conjugation with phenyl and quinazoline rings. H-5 appeared at δ_H 9.65 (d, $J_{5,7}$ = 2.1 Hz), showing *meta* coupling with H-7. Its downfield chemical shift is due to *ortho* NO_2 and N–C≡N groups. Similarly H-2 lying between the two electronegative nitrogen atoms of quinazoline nucleus, resonated at δ_H 8.69 (s). The remaining H-7 and H-8 of this

basic skeleton appeared as doublets at δ_H 8.56 (J = 9.3 Hz) and 7.93 (J = 9.3 Hz, 2.1 Hz), respectively. Four protons of *N*-phenyl ring (H-2′/H-6′ = δ_H 7.81) and (H-3′/H-5′ = δ_H 7.34), appeared as doublets (J = 8.7 Hz).

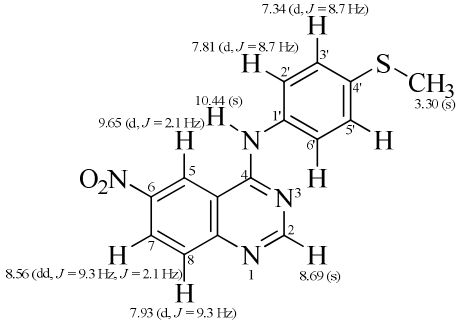


Figure-2: ^{1}H-NMR chemical shifts of compound **21**.

^{13}C-NMR broad-band decoupled spectrum (Figure-3) showed a total of 13 carbon signals, including 1 methyl, 6 methine, and 6 quarternary carbons. The quaternary carbon (C-4) lying between the two nitrogens, had the most downfield signal at δ_C 158.6. Second most downfield signal was assigned to C-2 (δ_C 157.6). This methine carbon is in between the two electronegative nitrogens of the quinazoline nucleus. C-6, *ipso* to nitro group, resonated at δ_C 144.4. Quaternary C-4′, adjacent to sulfur, appeared at δ_C 133.5. All remaining aromatic carbons in the structure appeared in the usual aromatic range of δ_C 114.3-153.0.

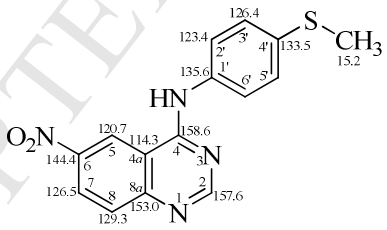


Figure-3: ^{13}C-NMR chemical shifts of compound **21.**

EI-MS of compound **21** (Figure-4) showed the molecular ion peak $[M]^+$ at *m/z* 312. The M^+ is also the base peak, indicating its stability. Loss of methyl radical yielded a peak at *m/z* 297. Neutral loss of $H_2C{=}S$ gave a radical cation at *m/z* 266. Cleavage of quinazoline ring generated a radical cation at *m/z* 164 which was further fragmented into cations at *m/z* 163 and 124, with the loss of hydrogen radical and N≡C–N, respectively.

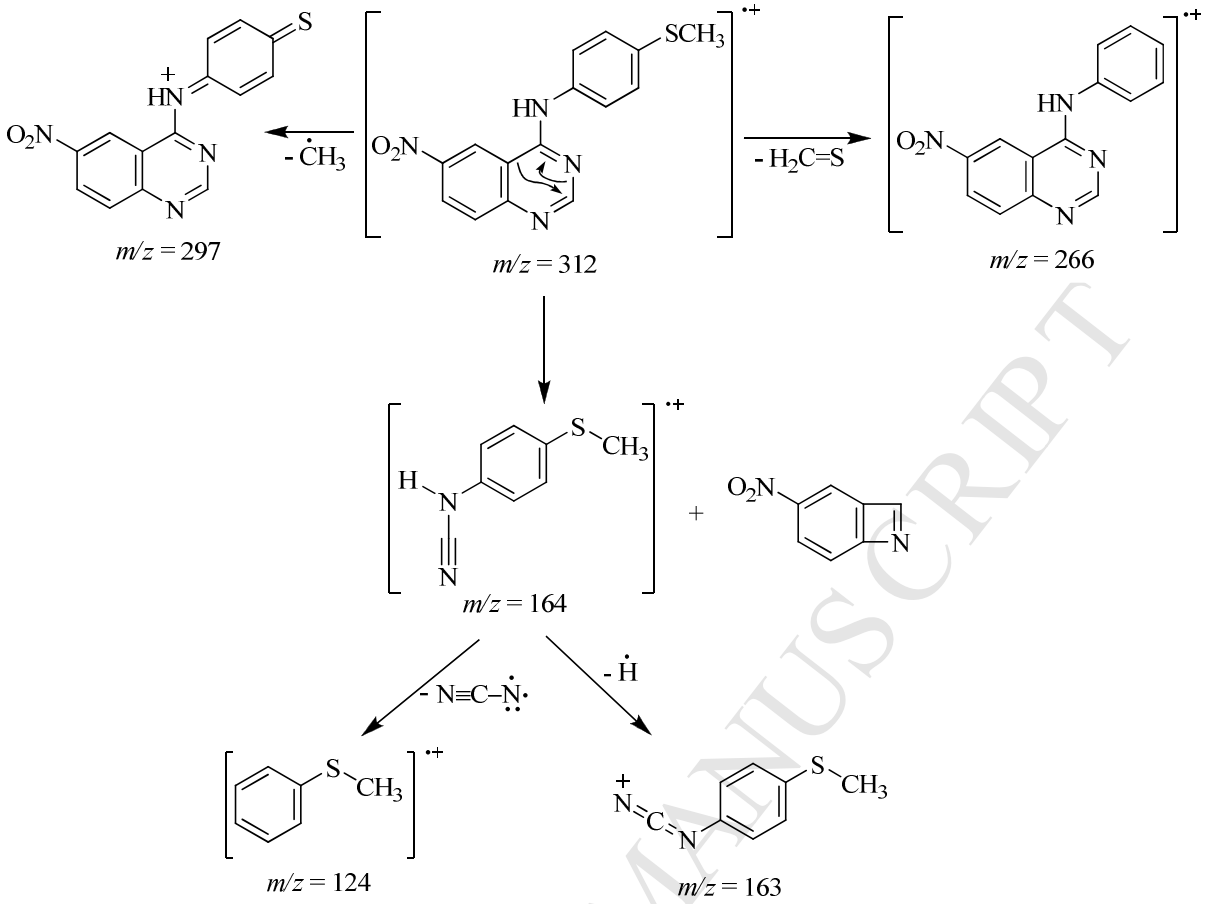


Figure-4: Key EI-MS fragmentation of compound **21**.

2.2. Antileishmanial Activities

The current study describes *in vitro* leishmanicidal activity, screening the antileishmanial potential of a broad range of 4-arylamino-6-nitroquinazoline compounds for the first time. We have screened compounds **2-25** against leismaniasis using pentamidine as a standard drug (IC_{50} ± SEM = 5.09 ± 0.09 μM) as per literature protocol [46]. Out of them, compounds **3**, **5**, **8**, **14-16**, **18**, **20-22**, and **24** were identified as good to moderate antileishmanial agents with IC_{50} values 61.48 ± 0.37, 24.03 ± 2.71, 4.37 ± 0.02, 19.87 ± 0.215, 9.04 ± 0.03, 6.53 ± 0.21, 12.28 ± 0.175, 38.17 ± 0.73, 1.87 ± 0.31, 44.91 ± 0.47, and 35.88 ± 0.185 μM, respectively (Table-1). 4-[4′-(Methylsulfanyl)phenyl]amino-6-nitroquinazoline (**21**) (IC_{50} = 1.87 ± 0.31 μM) and 4-(2′-methoxyphenyl)amino-6-nitroquinazoline (**8**) (IC_{50} = 4.37 ± 0.02 μM) were found to be more active than the standard, pentamidine (IC_{50} = 5.09 ± 0.09 μM). Compound **16** (IC_{50} = 6.53 ± 0.21 μM) displayed an activity comparable to the standard. Compounds **15** (IC_{50} = 9.04 ± 0.03 μM), **18** (IC_{50} = 12.28 ± 0.18 μM), **14** (IC_{50} = 19.87 ± 0.22 μM), and **5** (IC_{50} = 24.03 ± 2.71 μM) also demonstrated good activities. Compounds **24** (IC_{50} = 35. 88 ± 0.19 μM), **20** (IC_{50} = 38.17 ± 0.73 μM), **22** (IC_{50} = 44.91 ± 0.47 μM), and **3** (IC_{50} = 61.48 ±

0.37 μM) exhibited a weak activity. However, remaining compounds were found to be completely inactive.

Limited structure-activity relationship reveals that the difference in leishmanicidal strength of 4-arylamino-6-nitroquinazoline derivatives is a consequence of variations in substitutions on the 4-arylamino part of the molecule (Figure-5). A plausible reasoning is discussed below.

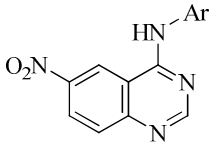


Figure-5: 4-Arylamino-6-nitroquinazoline **2-25**.

p-Methylsulfanyl substitution as in compound **21** (IC_{50} = 1.87 ± 0.31 μM) was found to be the most potent analog among the series when compared with standard pentamidine (IC_{50} = 5.09 ± 0.09 μM). It showed about three-fold more activity than the standard. The presence of methylsulfanyl substitution at *meta* position slightly lowered the activity as in compound **14** (IC_{50} = 19.87 ± 0.215 μM).

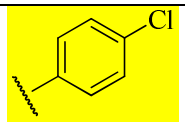
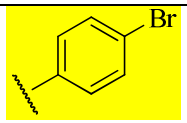
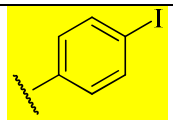
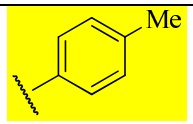
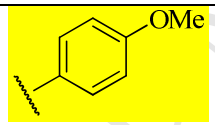
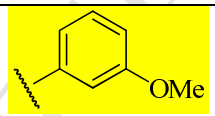
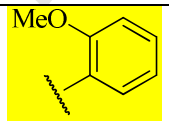
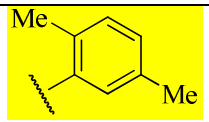
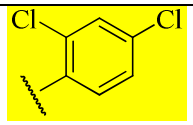
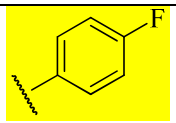
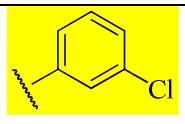
o-Methoxy substituted phenyl ring, as in compound **8**, showed an IC_{50} = 4.37 ± 0.02 μM more active than the standard drug. However, when the methoxy group was shifted to *meta* or *para* positions as in compounds **7** or **6**, respectively, the bioactivity entirely diminished. This clearly illustrates that methoxy group at the *ortho* position, plays an important role in activity. When another methoxy residue enters at its *para* position, as in compound **18** (IC_{50} = 12.28 ± 0.175 μM), it regains some leishmanicidal activity. Nonetheless, this time the bioactivity decreases to three-fold, as compared to parent compound **8**. The dimethoxy substituted analog lost its activity completely when a chlorine group is present at C-5′, as in compound **13**.

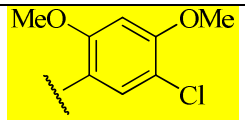
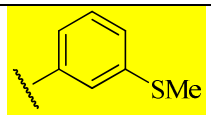
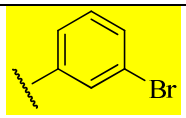
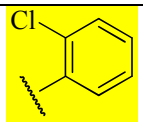
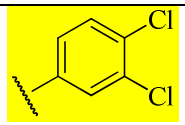
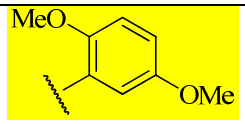
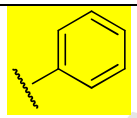
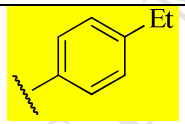
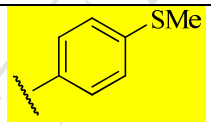
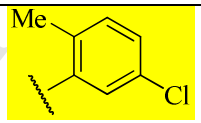
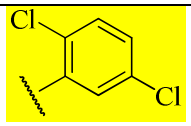
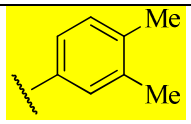
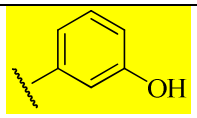
Substitution of methyl group at *para* position, as in compound **5** (IC_{50} = 24.03 ± 2.71 μM) revealed good leishmanicidal activity. A slight decrease in activity was observed when two methyl groups are present in an *ortho* fashion, as in compound **24** (IC_{50} = 35.88 ± 0.185 μM). While the two methyl groups *para* to each other, as in compound **9**, diminished all activity. When the methyl group of compound **5** was replaced with an ethyl group, as in compound **20** (IC_{50} = 38.17 ± 0.73 μM), the activity decreased.

Presence of a bromine at the *N*-phenyl ring, whether at *meta* position or at *para* position, as in compounds **15** or **3**, resulted in having a good antileishmanial effect with IC_{50} values 9.04 ±

0.03 and 61.48 ± 0.37 μM, respectively. The presence of fluorine (as in compound **11**), chlorine (as in compounds **2**, **10**, **12**, **17** and **23**) or iodine (as in compound **4**) decreased the activity. Surprisingly, only *o*-chlorinated analog **16** (IC_{50} = 6.53 ± 0.21 μM) displayed a comparable activity to standard pentamidine.

Table-1: Antileishmanial activity of 4-arylamino-6-nitroquinazolines (**2-25**).

Compounds	**Ar**	**IC_{50} ± SEM[a] [μM]**
2		N. A.[b]
3		61.48 ± 0.37
4		N. A.[b]
5		24.03 ± 2.71
6		N. A.[b]
7		N. A.[b]
8		4.37 ± 0.02
9		N. A.[b]
10		N. A.[b]
11		N. A.[b]
12		N. A.[b]

13		N. A.[b]
14		19.87 ± 0.22
15		9.04 ± 0.03
16		6.53 ± 0.21
17		N. A.[b]
18		12.28 ± 0.18
19		N. A.[b]
20		38.17 ± 0.73
21		1.87 ± 0.31
22		44.91 ± 0.47
23		N. A.[b]
24		35.88 ± 0.19
25		N. A.[b]
Standard	Pentamidine	5.09 ± 0.09

SEM[a] = Standard Error of the Mean, N. A.[b] = Not Active

3. Conclusion

We have prepared twenty-four substituted 4-arylamino-6-nitroquinazolines and evaluated their antileishmanial activities in comparison to the standard drug, pentamidine. Eleven compounds (**3**, **5**, **8**, **14-16**, **18**, **20-22**, and **24**) exhibited a good to moderate leishmanicidal effect with IC_{50} values 61.48 ± 0.37, 24.03 ± 2.71, 4.37 ± 0.02, 19.87 ± 0.215, 9.04 ± 0.03, 6.53 ± 0.21, 12.28 ± 0.175, 38.17 ± 0.73, 1.87 ± 0.31, 44.91 ± 0.47, and 35.88 ± 0.185 μM, respectively. These compounds deserve further research as a novel class of antileishmanial agents.

4. Experimental

4.1. Material and methods

Fetal Bovine Serum (Cat No. S181H-100 and Lot No. S11302S181H) was purchased from Biowest (The Serum Specialist). RPMI.1640 Liquid 20 mM HEPES, with L-glutatamine without $NaHCO_3$ (Cat No. 7388) was purchased from Sigma-Aldrich, USA. *Leishmania major* was acquired from DESTO. Neubauer counting chamber (2.5 x 10^{-3} mm^2) was purchased from Marienfeld, Germany. Standard drug, pentamidine was purchased from Merck, USA. 5-Nitroanthranilonitrile, dimethylformamide dimethylacetal, substituted anilines, and acetic acid were purchased from TCI, Japan. All reagents were of analytical grade and used directly without purification.

^{1}H NMR and ^{13}C NMR experiments were run on Avance Bruker AM 300, 400, and 500 MHz instruments. Electron Impact Mass Spectrometric (EI-MS) experiments were performed on Finnigan MAT-311A (Germany) mass spectrometer. Melting points were determined on Stuart® SMP10 melting point apparatus and are uncorrected. IR spectra (KBr discs) were run on FTS 3000 MX, Bio-RAD Merlin (Excalibur Model) spectrophotometer. CHN Analyses were carried out on a Carlo Erba Strumentazione-Mod-1106, Italy. Thin layer chromatography (TLC) was performed on pre-coated silica gel aluminum plates (Kieselgel 60, 254, E. Merck, Germany). TLC Chromatograms were visualized under UV light at 254 and 365 nm or by applying iodine vapours.

4.2. Assay for Leishmaniasis [46]

Leishmania major were grown in bulk in modified *N,N,N*-biphasic medium by using normal physiological saline. *Leishmania* promastigotes were cultured with RPMI 1640 medium, supplemented with 10% heat inactivated fetal bovine serum (FBS). Parasites at log phase

were centrifuged at 2000 rpm for 10 min, and washed three times with saline at same speed and time. Parasites were diluted with fresh culture medium to a final density of 10^6 cells/mL. In a 96-well micro-titer plate, 180 μL of medium was added in the first row and 100 μL of medium was added in other wells. 20 μL of the experimental compounds were added in medium, serially diluted. 100 μL of parasite culture was also added in all wells. Two rows were left for negative and positive controls. Negative controls received only medium, while the positive control contained varying concentrations of standard antileishmanial compound, pentamidine. The plates were incubated 21-22 °C for 72 h. The culture was examined microscopically on an improved Neubauer counting chamber and IC_{50} values of compounds were calculated by Software Ezfit 5.03 Perella Scientific. All assays were performed in triplicate.

4.3. Procedure for the synthesis of compounds 1-25

(*E*)-*N*'-(2-Cyano-4-nitrophenyl)-*N*,*N*-dimethylformimidamide (**1**) was synthesized as per method reported earlier [45]. 4-Arylamino-6-nitroquinazolines (**2-25**) were synthesized by treating substituted anilines (2 mmol) with (*E*)-*N*'-(2-cyano-4-nitrophenyl)-*N*,*N*-dimethylformimidamide (**1**) (2 mmol) in acetic acid (15 mL) under refluxing condition. Progress of the reaction mixture was monitored by thin layer chromatography. After completion of the reaction, the reaction mixture was cooled to room temperature and distilled water was added and shaken until the precipitates appeared. These precipitates were filtered and washed with water. The yields of title compounds were found to be moderate to high.

4.3.1. (*E*)-*N*′-(2-Cyano-4-nitrophenyl)-*N*,*N*-dimethylformimidamide (1)

Yield: 94%; m.p. 152-153 °C (lit. 153-155 °C [41]); R_f: 0.24 (ethyl acetate/hexaness, 3:7); ^{1}H-NMR: (500 MHz, DMSO-d_6): δ_H 8.47 (d, 1H, $J_{3,5}$ = 2.5 Hz, H-3), 8.28 (dd, 1H, $J_{5,6}$ = 9.0 Hz, $J_{5,3}$ = 3.0 Hz, H-5), 8.27 (s, 1H, N=CH), 7.38 (d, 1H, $J_{6,5}$ = 9.5 Hz, H-6), 3.15 (s, 3H, NCH_3), 3.07 (s, 3H, NCH_3); ^{13}C-NMR: (100 MHz, DMSO-d_6): δ_c 160.4 (C-1), 156.6 (C=N), 140.0 (C-4), 129.4 (C-3), 128.5 (C-5), 118.3 (C-6), 116.7 (C≡N), 105.8 (C-2), 34.3 (H_3C-N); IR (KBr, cm^{-1}): 2222 (C≡N), 1630 (C=N), 1502 (N=O); EI-MS: *m/z* (rel. abund. %), 218 $[M]^+$ (100), 203 (14), 172 (8); HREI-MS: *m/z* calcd for $C_{10}H_{10}N_4O_2$ $[M]^+$ 218.0804; Found 218.0802; Anal. Calcd for $C_{10}H_{10}N_4O_2$: C, 55.04; H, 4.62; N, 25.68; O, 14.66; Found: C, 55.02; H, 4.64; N, 25.69.

4.3.2. 4-(4′-Chlorophenyl)amino-6-nitroquinazoline (2)

Yield: 92%; m.p. 264-265 °C (lit. 264 °C [41]); R_f: 0.46 (ethyl acetate/hexanes, 3:7); ^{1}H-NMR: (300 MHz, DMSO-*d*$_6$): δ_H 10.50 (s, 1H, NH), 9.66 (d, 1H, $J_{5,7}$ = 2.1 Hz, H-5), 8.73 (s, 1H, H-2), 8.58 (dd, 1H, $J_{7,8}$ = 9.0 Hz, $J_{7,5}$ = 2.1 Hz, H-7), 7.96 (d, 1H, $J_{8,7}$ = 9.0 Hz, H-8), 7.91 (d, 2H, $J_{2',3'} = J_{6',5'}$ = 8.7 Hz, H-2′, H-6′), 7.49 (d, 2H, $J_{3',2'} = J_{5',6'}$ = 8.7 Hz, H-3′, H-5′); ^{13}C-NMR: (100 MHz, DMSO-*d*$_6$): δ_c 158.6 (C-4), 157.5 (C-2), 153.0 (C-8*a*), 144.5 (C-6), 137.4 (C-1′), 129.5 (C-8), 128.4 (C-4′), 128.1 (C-3′, C-5′), 126.6 (C-7), 124.3 (C-2′, C-6′), 120.8 (C-5), 114.3 (C-4*a*); IR (KBr, cm^{-1}): 3416 (N–H), 1622 (C=N), 1539 (N=O), 1109 (C–Cl); EI-MS: *m/z* (rel. abund. %), 302 [M$^+$+2] (26), 300 [M]$^+$ (77), 299 (100), 253 (58); HREI-MS: *m/z* calcd for $C_{14}H_9ClN_4O_2$ [M]$^+$ 300.0414; Found 300.0410; Anal. Calcd for $C_{14}H_9ClN_4O_2$: C, 55.92; H, 3.02; Cl, 11.79; N, 18.63; O, 10.64; Found: C, 55.90; H, 3.04; N, 18.61.

4.3.3. 4-(4′-Bromophenyl)amino-6-nitroquinazoline (3)

Yield: 82%; m.p. 278-280 °C (lit. 279-280 °C [42]); R_f: 0.47 (ethyl acetate/hexanes, 3:7); ^{1}H-NMR: (300 MHz, DMSO-*d*$_6$): δ_H 10.49 (s, 1H, NH), 9.66 (d, 1H, $J_{5,7}$ = 2.1 Hz, H-5), 8.73 (s, 1H, H-2), 8.58 (dd, 1H, $J_{7,8}$ = 9.0 Hz, $J_{7,5}$ = 2.1 Hz, H-7), 7.96 (d, 1H, $J_{8,7}$ = 8.1 Hz, H-8), 7.86 (d, 2H, $J_{2',3'} = J_{6',5'}$ = 8.7 Hz, H-2′, H-6′), 7.62 (d, 2H, $J_{3',2'} = J_{5',6'}$ = 8.7 Hz, H-3′, H-5′); ^{13}C-NMR: (75 MHz, DMSO-*d*$_6$): δ_c 158.6 (C-4), 157.4 (C-2), 152.9 (C-8*a*), 144.5 (C-6), 137.8 (C-1′), 131.3 (C-8), 129.5 (C-3′, C-5′), 126.6 (C-7), 124.6 (C-2′, C-6′), 120.8 (C-5), 116.2 (C-4′), 114.4 (C-4*a*); IR (KBr, cm^{-1}): 3416 (N–H), 1616 (C=N), 1537 (N=O), 743 (C–Br); EI-MS: *m/z* (rel. abund. %), 346 [M$^+$+2] (83), 345 (100), 344 [M]$^+$ (84), 343 (80), 299 (39), 297 (39); HREI-MS: *m/z* calcd for $C_{14}H_9BrN_4O_2$ [M]$^+$ 343.9909; Found 343.9892; Anal. Calcd for $C_{14}H_9BrN_4O_2$: C, 48.72; H, 2.63; Br, 23.15; N, 16.23; O, 9.27; Found: C, 48.70; H, 2.61; N, 16.25.

4.3.4. 4-(4′-Iodophenyl)amino-6-nitroquinazoline (4)

Yield: 83%; m.p. 270 °C; R_f: 0.48 (ethyl acetate/hexanes, 3:7); ^{1}H-NMR: (300 MHz, DMSO-*d*$_6$): δ_H 10.46 (s, 1H, NH), 9.66 (d, 1H, $J_{5,7}$ = 2.1 Hz, H-5), 8.73 (s, 1H, H-2), 8.58 (dd, 1H, $J_{7,8}$ = 9.3 Hz, $J_{7,5}$ = 2.1 Hz, H-7), 7.96 (d, 1H, $J_{8,7}$ = 9.0 Hz, H-8), 7.78 (d, 2H, $J_{2',3'} = J_{6',5'}$ = 8.7 Hz, H-2′, H-6′), 7.72 (d, 2H, $J_{3',2'} = J_{5',6'}$ = 8.7 Hz, H-3′, H-5′); ^{13}C-NMR: (100 MHz, DMSO-*d*$_6$): δ_c 158.6 (C-4), 157.5 (C-2), 153.0 (C-8*a*), 144.5 (C-6), 138.3 (C-1′), 137.1 (C-8), 129.5 (C-3′, C-5′), 126.6 (C-7), 124.8 (C-2′, C-6′), 120.8 (C-5), 114.4 (C-4*a*), 88.4 (C-4′); IR (KBr, cm^{-1}): 3280 (N–H), 1626 (C=N), 1528 (N=O), 544 (C–I); EI-MS: *m/z* (rel. abund. %), 392 [M]$^+$ (100), 391 (89), 345 (34), 265 (2), 218 (28); HREI-MS: *m/z* calcd for $C_{14}H_9IN_4O_2$

$[M]^+$ 391.9770; Found 391.9785; Anal. Calcd for $C_{14}H_9IN_4O_2$: C, 42.88; H, 2.31; I, 32.36; N, 14.29; O, 8.16; Found: C, 42.86; H, 2.30; N, 14.31.

4.3.5. 4-(4′-Methylphenyl)amino-6-nitroquinazoline (5)

Yield: 90%; m.p. 208-210 °C (lit. 210 °C [43]); R_f: 0.38 (ethyl acetate/hexanes, 3:7); ^{1}H-NMR: (300 MHz, DMSO-d_6): δ_H 10.40 (s, 1H, NH), 9.65 (d, 1H, $J_{5,7}$ = 2.1 Hz, H-5), 8.67 (s, 1H, H-2), 8.56 (dd, 1H, $J_{7,8}$ = 9.0 Hz, $J_{7,5}$ = 2.1 Hz, H-7), 7.92 (d, 1H, $J_{8,7}$ = 9.3 Hz, H-8), 7.70 (d, 2H, $J_{2',3'}$ = $J_{6',5'}$ = 8.1 Hz, H-2′, H-6′), 7.24 (d, 2H, $J_{3',2'}$ = $J_{5',6'}$ = 8.1 Hz, H-3′, H-5′), 2.31 (s, 3H, 4′-CH_3); ^{13}C-NMR: (75 MHz, DMSO-d_6): δ_c 158.8 (C-4), 157.7 (C-2), 153.0 (C-8*a*), 144.4 (C-6), 135.7 (C-1′), 133.7 (C-4′), 129.4 (C-8), 128.9 (C-3′, C-5′), 126.5 (C-7), 122.9 (C-2′, C-6′), 120.8 (C-5), 114.3 (C-4*a*), 20.5 (4′-CH_3); IR (KBr, cm^{-1}): 3620 (N–H), 1620 (C=N), 1529 (N=O); EI-MS: *m/z* (rel. abund. %), 280 $[M]^+$ (96), 279 (100), 233 (72), 106 (7), 91 (6); HREI-MS: *m/z* calcd for $C_{15}H_{12}N_4O_2$ $[M]^+$ 280.0960; Found 280.0950; Anal. Calcd for $C_{15}H_{12}N_4O_2$: C, 64.28; H, 4.32; N, 19.99; O, 11.42; Found: C, 64.26; H, 4.35; N, 19.97.

4.3.6. 4-(4′-Methoxyphenyl)amino-6-nitroquinazoline (6)

Yield: Quantitative; m.p. 197-199 °C (lit. 198-200 °C [43]); R_f: 0.29 (ethyl acetate/hexanes, 3:7); ^{1}H-NMR: (300 MHz, DMSO-d_6): δ_H 10.38 (s, 1H, NH), 9.62 (d, 1H, $J_{5,7}$ = 2.1 Hz, H-5), 8.63 (s, 1H, H-2), 8.54 (dd, 1H, $J_{7,8}$ = 9.0 Hz, $J_{7,5}$ = 2.1 Hz, H-7), 7.91 (d, 1H, $J_{8,7}$ = 9.3 Hz, H-8), 7.69 (d, 2H, $J_{2',3'}$ = $J_{6',5'}$ = 9.0 Hz, H-2′, H-6′), 7.00 (d, 2H, $J_{3',2'}$ = $J_{5',6'}$ = 9.0 Hz, H-3′, H-5′), 3.77 (s, 3H, 4′-OCH_3); ^{13}C-NMR: (100 MHz, DMSO-d_6): δ_c 158.8 (C-4), 157.8 (C-2), 156.3 (C-4′), 153.0 (C-8*a*), 144.3 (C-6), 131.0 (C-1′), 129.3 (C-8), 126.4 (C-7), 124.6 (C-2′, C-6′), 120.7 (C-5), 114.2 (C-4*a*), 113.7 (C-3′, C-5′), 55.2 (4′-OCH_3); IR (KBr, cm^{-1}): 3622 (N–H), 1622 (C=N), 1526 (N=O), 1236 (C–O); EI-MS: *m/z* (rel. abund. %), 296 $[M]^+$ (100), 295 (49), 281 (50), 249 (19); HREI-MS: *m/z* calcd for $C_{15}H_{12}N_4O_3$ $[M]^+$ 296.0909; Found 296.0923; Anal. Calcd for $C_{15}H_{12}N_4O_3$: C, 60.81; H, 4.08; N, 18.91; O, 16.20; Found: C, 60.83; H, 4.06; N, 18.93.

4.3.7. 4-(3′-Methoxyphenyl)amino-6-nitroquinazoline (7)

Yield: 88%; m.p. 242 °C (lit. 241-242 °C [42]); R_f: 0.46 (ethyl acetate/hexanes, 3:7); ^{1}H-NMR: (300 MHz, DMSO-d_6): δ_H 10.39 (s, 1H, NH), 9.67 (d, 1H, $J_{5,7}$ = 2.1 Hz, H-5), 8.73 (s, 1H, H-2), 8.57 (dd, 1H, $J_{7,8}$ = 9.3 Hz, $J_{7,5}$ = 2.1 Hz, H-7), 7.95 (d, 1H, $J_{8,7}$ = 9.3 Hz, H-8), 7.50 (m, 2H, H-2′, H-6′), 7.35 (t, 1H, $J_{5'(4',6')}$ = 8.1 Hz, H-5′), 6.79 (dd, 1H, $J_{4',5'}$ = 8.1 Hz, $J_{4',6'}$ = 1.8 Hz,

H-4′), 3.78 (s, 3H, 3′-OCH_3); ^{13}C-NMR: (75 MHz, DMSO-d_6): δ_c 159.3 (C-4), 158.7 (C-3′), 157.6 (C-2), 153.0 (C-8*a*), 144.5 (C-6), 139.5 (C-1′), 129.4 (C-8), 129.2 (C-7), 126.5 (C-5′), 120.8 (C-5), 115.0 (C-4′), 114.4 (C-4*a*), 109.8 (C-6′), 108.6 (C-2′), 55.1 (3′-OCH_3); IR (KBr, cm^{-1}): 3298 (N–H), 1624 (C=N), 1528 (N=O), 1227 (C–O); EI-MS: *m/z* (rel. abund. %), 296 $[M]^+$ (95), 295 (100), 281 (4), 249 (63); HREI-MS: *m/z* calcd for $C_{15}H_{12}N_4O_3$ $[M]^+$ 296.0909; Found 296.0928; Anal. Calcd for $C_{15}H_{12}N_4O_3$: C, 60.75; H, 4.08; N, 18.91; O, 16.20; Found: C, 60.78; H, 4.10; N, 18.92.

4.3.8. 4-(2′-Methoxyphenyl)amino-6-nitroquinazoline (8)

Yield: 74%; m.p. 215 °C; R_f: 0.36 (ethyl acetate/hexanes, 3:7); ^{1}H-NMR: (300 MHz, DMSO-d_6): δ_H 10.24 (s, 1H, NH), 9.60 (d, 1H, $J_{5,7}$ = 2.1 Hz, H-5), 8.55 (m, 2H, H-7, H-2), 7.91 (d, 1H, $J_{8,7}$ = 9.3 Hz, H-8), 7.44 (d, 1H, $J_{6',5'}$ = 6.9 Hz, H-6′), 7.33 (t, 1H, $J_{5'(4',6')}$ = 7.2 Hz, H-5′), 7.16 (d, 1H, $J_{3',4'}$ = 7.8 Hz, H-3′), 7.03 (t, 1H, $J_{4'(3',5')}$ = 7.5 Hz, H-4′), 3.76 (s, 3H, 2′-OCH_3); ^{13}C-NMR: (100 MHz, DMSO-d_6): δ_c 160.0 (C-4), 158.0 (C-2), 154.1 (C-2′), 153.0 (C-8*a*), 144.3 (C-6), 129.3 (C-8), 128.0 (C-7), 127.6 (C-4′), 126.5 (C-5), 126.2 (C-1′),120.9 (C-5′), 120.2 (C-3′), 114.0 (C-4*a*), 112.1 (C-6′), 55.5 (2′-OCH_3); IR (KBr, cm^{-1}): 3289 (N–H), 1616 (C=N), 1533 (N=O), 1242 (C–O); EI-MS: *m/z* (rel. abund. %), 296 $[M]^+$ (7), 281 (2), 265 (100), 249 (5), 235 (34), 219 (46); HREI-MS: *m/z* calcd for $C_{15}H_{12}N_4O_3$ $[M]^+$ 296.0909; Found 296.0928; Anal. Calcd for $C_{15}H_{12}N_4O_3$: C, 60.81; H, 4.08; N, 18.91; O, 16.20; Found: C, 60.83; H, 4.11; N, 18.94.

4.3.9. 4-(2′,5′-Dimethylphenyl)amino-6-nitroquinazoline (9)

Yield: 43%; m.p. 145 °C; R_f: 0.40 (ethyl acetate/hexanes, 3:7); ^{1}H-NMR: (300 MHz, DMSO-d_6): δ_H 10.35 (s, 1H, NH), 9.58 (d, 1H, $J_{5,7}$ = 2.4 Hz, H-5), 8.56 (m, 2H, H-7, H-2), 7.92 (d, 1H, $J_{8,7}$ = 9.0 Hz, H-8), 7.22 (d, 1H, $J_{3',4'}$ = 7.8 Hz, H-3′), 7.11 (m, 2H, H-4′, H-6′), 2.29 (s, 3H, 5′-CH_3), 2.12 (s, 3H, 2′-CH_3); ^{13}C-NMR: (100 MHz, DMSO-d_6): δ_c 159.9 (C-4), 158.1 (C-2), 153.0 (C-8*a*), 144.3 (C-6), 136.2 (C-5′), 135.4 (C-2′), 131.7 (C-1′), 130.3 (C-3′), 129.3 (C-8), 127.9 (C-7), 127.5 (C-5),126.5 (C-4′), 120.9 (C-6′), 113.9 (C-4*a*), 20.4 (5′-CH_3), 17.5 (2′-CH_3); IR (KBr, cm^{-1}): 3616 (N–H), 1622 (C=N), 1531 (N=O); EI-MS: *m/z* (rel. abund. %), 294 $[M]^+$ (100), 279 (98), 247 (40), 233 (60), 120 (20); HREI-MS: *m/z* calcd for $C_{16}H_{14}N_4O_2$ $[M]^+$ 294.1117; Found 294.1125; Anal. Calcd for $C_{16}H_{14}N_4O_2$: C, 65.30; H, 4.79; N, 19.04; O, 10.87; Found: C, 65.32; H, 4.81; N, 19.06.

4.3.10. 4-(2′,4′-Dichlorophenyl)amino-6-nitroquinazoline (10)

Yield: 49%; m.p. 255-257 °C (lit. 256-258 °C [41]); R_f: 0.47 (ethyl acetate/hexanes, 3:7); ^{1}H-NMR: (300 MHz, DMSO-d_6): δ_H 10.64 (s, 1H, NH), 9.56 (s, 1H, H-5), 8.57 (m, 2H, H-7, H-8), 8.00 (m, 1H, H-5′), 7.82 (m, 1H, H-6′), 7.52 (m, 2H, H-2, H-3′); ^{13}C-NMR: (100 MHz, DMSO-d_6): δ_c 158.6 (C-4), 157.7 (C-2), 152.9 (C-8*a*), 144.6 (C-6), 139.9 (C-1′), 134.4 (C-5′), 132.7 (C-3′), 130.1 (C-2′), 129.3 (C-8), 127.9 (C-4′), 126.8 (C-7), 125.7 (C-6′), 120.9 (C-5), 114.3 (C-4*a*); IR (KBr, cm^{-1}): 3402 (N–H), 1618 (C=N), 1524 (N=O), 1105 (C–Cl); EI-MS: *m/z* (rel. abund. %), 338 [M^++4] (2), 336 [M^++2] (7), 334 $[M]^+$ (9), 299 (100), 265 (52), 253 (72); HREI-MS: *m/z* calcd for $C_{14}H_8Cl_2N_4O_2$ $[M]^+$ 334.0024; Found 334.0026; Anal. Calcd for $C_{14}H_8Cl_2N_4O_2$: C, 50.17; H, 2.41; Cl, 21.16; N, 16.72; O, 9.55; Found: C, 50.15; H, 2.42; N, 16.74.

4.3.11. 4-(4′-Fluorophenyl)amino-6-nitroquinazoline (11)

Yield: 96%; m.p. 257-258 °C (lit. 257-258 °C [42]); R_f: 0.46 (ethyl acetate/hexanes, 3:7); ^{1}H-NMR: (300 MHz, DMSO-d_6): δ_H 10.48 (s, 1H, NH), 9.64 (d, 1H, $J_{5,7}$ = 2.4 Hz, H-5), 8.69 (s, 1H, H-2), 8.57 (dd, 1H, $J_{7,8}$ = 9.3 Hz, $J_{7,5}$ = 2.4 Hz, H-7), 7.95 (d, 1H, $J_{8,7}$ = 9.3 Hz, H-8), 7.85 (d, 2H, $J_{2',3'} = J_{6',5'}$ = 8.7 Hz, H-2′, H-6′), 7.29 (t, 2H, $J_{3'(2',F)} = J_{5'(6',F)}$ = 8.7 Hz, H-3′, H-5′); ^{13}C-NMR: (125 MHz, DMSO-d_6): δ_c 159.8 (C-4), 158.8 (C-4′), 157.6 (C-2), 153.0 (C-8*a*), 144.4 (C-6), 134.6 (C-1′), 129.4 (C-8), 126.6 (C-7), 125.0 (C-2′, C-6′), 120.7 (C-5), 115.2 (C-3′, C-5′), 114.2 (4*a*); IR (KBr, cm^{-1}): 3624 (N–H), 1624 (C=N), 1537 (N=O), 1223 (C–F); EI-MS: *m/z* (rel. abund. %), 284 $[M]^+$ (98), 283 (100), 265 (2), 253 (11), 237 (87); HREI-MS: *m/z* calcd for $C_{14}H_9FN_4O_2$ $[M]^+$ 284.0710; Found 284.0697; Anal. Calcd for $C_{14}H_9FN_4O_2$: C, 59.16; H, 3.19; F, 6.68; N, 19.71; O, 11.26; Found: C, 59.17; H, 3.16; N, 19.70.

4.3.12. 4-(3′-Chlorophenyl)amino-6-nitroquinazoline (12)

Yield: 93%; m.p. 284-286 °C (lit. 285-286 °C [42]); R_f: 0.32 (ethyl acetate/hexanes, 3:7); ^{1}H-NMR: (300 MHz, DMSO-d_6): δ_H 10.49 (s, 1H, NH), 9.66 (d, 1H, $J_{5,7}$ = 1.8 Hz, H-5), 8.78 (s, 1H, H-2), 8.58 (dd, 1H, $J_{7,8}$ = 9.3 Hz, $J_{7,5}$ = 1.8 Hz, H-7), 8.07 (s, 1H, H-2′), 7.97 (d, 1H, $J_{8,7}$ = 9.3 Hz, H-8), 7.85 (d, 1H, $J_{6',5'}$ = 7.8 Hz, H-6′), 7.47 (t, 1H, $J_{5'(4',6')}$ = 8.1 Hz, H-5′), 7.24 (d, 1H, $J_{4',5'}$ = 7.8 Hz, H-4′); ^{13}C-NMR: (100 MHz, DMSO-d_6): δ_c 158.6 (C-4), 157.4 (C-2), 152.9 (C-8*a*), 144.6 (C-6), 139.9 (C-1′), 132.7 (C-3′), 130.1 (C-5′), 129.5 (C-8), 126.6 (C-7), 123.9 (C-4′), 121.9 (C-2′), 120.8 (C-5), 120.7 (C-6′), 114.3 (C-4*a*); IR (KBr, cm^{-1}): 3287 (N–H), 1620 (C=N), 1528 (N=O), 1109 (C–Cl); EI-MS: *m/z* (rel. abund. %), 302 [M^++2] (18), 300 $[M]^+$ (57), 299 (100), 253 (85); HREI-MS: *m/z* calcd for $C_{14}H_9ClN_4O_2$ $[M]^+$ 300.0414;

Found 300.0424; Anal. Calcd for $C_{14}H_9ClN_4O_2$: C, 55.92; H, 3.02; Cl, 11.79; N, 18.63; O, 10.64; Found: C, 55.90; H, 3.04; N, 18.65.

4.3.13. 4-(5′-Chloro-2′,4′-dimethoxyphenyl)amino-6-nitroquinazoline (13)

Yield: Quantitative; m.p. 232-235 °C; R_f: 0.10 (ethyl acetate/hexanes, 3:7); ^{1}H-NMR: (300 MHz, DMSO-d_6): δ_H 10.18 (s, 1H, NH), 9.57 (d, 1H, $J_{5,7}$ = 2.1 Hz, H-5), 8.54 (m, 2H, H-7, H-2), 7.91 (d, 1H, $J_{8,7}$ = 9.3 Hz, H-8), 7.46 (s, 1H, H-6′), 6.91 (s, 1H, H-3′), 3.94 (s, 3H, 4′-OCH_3), 3.82 (s, 3H, 2′-OCH_3); ^{13}C-NMR: (100 MHz, DMSO-d_6): δ_c 160.2 (C-4), 158.0 (C-2), 154.2 (C-4′), 153.9 (C-2′), 152.9 (C-8*a*), 144.3 (C-6), 129.3 (C-8), 128.7 (C-6′), 126.5 (C-7), 120.8 (C-5), 119.1 (C-1′), 113.9 (C-4*a*), 111.1 (C-5′), 98.2 (C-3′), 56.4 (2′-OCH_3), 56.1 (4′-OCH_3); IR (KBr, cm^{-1}): 3414 (N–H), 1593 (C=N), 1533 (N=O), 1256 (C–O), 1109 (C–Cl); EI-MS: *m/z* (rel. abund. %), 362 [M$^+$+2] (11), 360 [M]$^+$ (29), 345 (8), 329 (100); HREI-MS: *m/z* calcd for $C_{16}H_{13}ClN_4O_4$ [M]$^+$ 360.0625; Found 360.0644; Anal. Calcd for $C_{16}H_{13}ClN_4O_4$: C, 53.27; H, 3.63; Cl, 9.83; N, 15.53; O, 17.74; Found: C, 53.28; H, 3.61; N, 15.55.

4.3.14. 4-[3′-(Methylsulfanyl)phenyl]amino-6-nitroquinazoline (14)

Yield: 60%; m.p. 196-197 °C; R_f: 0.32 (ethyl acetate/hexanes, 3:7); ^{1}H-NMR: (300 MHz, DMSO-d_6): δ_H 10.41 (s, 1H, NH), 9.66 (d, 1H, $J_{5,7}$ = 1.8 Hz, H-5), 8.74 (s, 1H, H-2), 8.58 (dd, 1H, $J_{7,8}$ = 9.0 Hz, $J_{7,5}$ = 1.8 Hz, H-7), 7.96 (d, 1H, $J_{8,7}$ = 9.0 Hz, H-8), 7.77 (s, 1H, H-2′), 7.69 (d, 1H, $J_{6',5'}$ = 7.8 Hz, H-6′), 7.39 (t, 1H, $J_{5'(4',6')}$ = 8.1 Hz, H-5′), 7.09 (d, 1H, $J_{4',5'}$ = 7.8 Hz, H-4′), 3.29 (s, 3H, 3′-SCH_3); ^{13}C-NMR: (100 MHz, DMSO-d_6): δ_c 158.7 (C-4), 157.6 (C-2), 153.0 (C-8*a*), 144.5 (C-6), 139.0 (C-1′), 138.4 (C-3′), 129.5 (C-8), 129.0 (C-5′), 126.6 (C-7), 121.8 (C-4′), 120.8 (C-5), 119.9 (C-6′), 119.3 (C-2′), 114.4 (C-4*a*), 14.8 (3′-SCH_3); IR (KBr, cm^{-1}): 3609 (N–H), 1576 (C=N), 1533 (N=O), 1117 (C–S); EI-MS: *m/z* (rel. abund. %), 312 [M]$^+$ (100), 311 (98), 297 (3), 265 (43); HREI-MS: *m/z* calcd for $C_{15}H_{12}N_4O_2S$ [M]$^+$ 312.0681; Found 312.0675; Anal. Calcd for $C_{15}H_{12}N_4O_2S$: C, 57.68; H, 3.87; N, 17.94; O, 10.24; S, 10.27; Found: C, 57.69; H, 3.89; N, 17.93.

4.3.15. 4-(3′-Bromophenyl)amino-6-nitroquinazoline (15)

Yield: 82%; m.p. 269-271 °C (lit. 267-270 °C [41]); R_f: 0.64 (ethyl acetate/hexanes, 3:7); ^{1}H-NMR: (300 MHz, DMSO-d_6): δ_H 10.49 (s, 1H, NH), 9.67 (d, 1H, $J_{5,7}$ = 1.8 Hz, H-5), 8.78 (s, 1H, H-2), 8.59 (dd, 1H, $J_{7,8}$ = 9.0 Hz, $J_{7,5}$ = 1.8 Hz, H-7), 8.19 (s, 1H, H-2′), 7.98 (d, 1H, $J_{8,7}$ = 9.3 Hz, H-8), 7.92 (d, 1H, $J_{6',5'}$ = 6.9 Hz, H-6′), 7.39 (m, 2H, H-4′, H-5′); ^{13}C-NMR: (100 MHz, DMSO-d_6): δ_c 158.5 (C-4), 157.4 (C-2), 152.9 (C-8*a*), 144.5 (C-6), 140.1 (C-1′), 130.4

(C-5′), 129.5 (C-8), 126.8 (C-4′), 126.6 (C-7), 124.7 (C-6′), 121.2 (C-2′), 121.1 (C-3′), 120.7 (C-5), 114.3 (C-4*a*); IR (KBr, cm^{-1}): 3300 (N–H), 1618 (C=N), 1524 (N=O), 745 (C–Br); EI-MS: *m/z* (rel. abund. %), 346 [M^++2] (57), 345 (100), 344 $[M]^+$ (63), 343 (97), 299 (46), 297 (46); HREI-MS: *m/z* calcd for $C_{14}H_9BrN_4O_2$ $[M]^+$ 343.9909; Found 343.9799; Anal. Calcd for $C_{14}H_9BrN_4O_2$: C, 48.72; H, 2.63; Br, 23.15; N, 16.23; O, 9.27; Found: C, 48.74; H, 2.62; N, 16.25.

4.3.16. 4-(2′-Chlorophenyl)amino-6-nitroquinazoline (16)

Yield: 44%; m.p. 181-182 °C (lit. 180-182 °C [41]); R_f: 0.34 (ethyl acetate/hexanes, 3:7); ^{1}H-NMR: (300 MHz, DMSO-d_6): δ_H 10.63 (s, 1H, NH), 9.60 (s, 1H, H-5), 8.58 (m, 2H, H-7, H-2), 7.96 (d, 1H, $J_{8,7}$ = 8.7 Hz, H-8), 7.62 (m, 2H, H-6′, H-3′), 7.46 (m, 2H, H-4′, H-5′); ^{13}C-NMR: (100 MHz, DMSO-d_6): δ_c 158.6 (C-4), 157.5 (C-2), 153.0 (C-8*a*), 144.5 (C-6), 137.4 (C-1′), 134.4 (C-3′), 131.2 (C-5′), 129.8 (C-8), 128.4 (C-7), 127.8 (C-4′), 126.7 (C-2′), 124.3 (C-5), 120.9 (C-6′), 114.3 (C-4*a*); IR (KBr, cm^{-1}): 3362 (N–H), 1620 (C=N), 1512 (N=O), 1115 (C–Cl); EI-MS: *m/z* (rel. abund. %), 302 [M^++2] (4), 300 $[M]^+$ (9), 265 (100), 219 (73); HREI-MS: *m/z* calcd for $C_{14}H_9ClN_4O_2$ $[M]^+$ 300.0414; Found 300.0397; Anal. Calcd for $C_{14}H_9ClN_4O_2$: C, 55.92; H, 3.02; Cl, 11.79; N, 18.63; O, 10.64; Found: C, 55.94; H, 3.04; N, 18.66.

4.3.17. 4-(3′,4′-Dichlorophenyl)amino-6-nitroquinazoline (17)

Yield: 66%; m.p. 297-298 °C (lit. 297-298 °C [42]); R_f: 0.16 (ethyl acetate/hexanes, 3:7); ^{1}H-NMR: (300 MHz, DMSO-d_6): δ_H 10.53 (s, 1H, NH), 9.65 (d, 1H, $J_{5,7}$ = 2.4 Hz, H-5), 8.08 (s, 1H, H-2), 8.59 (dd, 1H, $J_{7,8}$ = 9.3 Hz, $J_{7,5}$ = 2.4 Hz, H-7), 8.29 (d, 1H, $J_{2',6'}$ = 1.8 Hz, H-2′), 7.98 (d, 1H, $J_{8',7'}$ = 9.3 Hz, H-8′), 7.93 (dd, 1H, $J_{6',5'}$ = 8.7 Hz, $J_{6',2'}$ = 1.8 Hz, H-6′), 7.69 (d, 1H, $J_{5',6'}$ = 8.7 Hz, H-5′); ^{13}C-NMR: (100 MHz, DMSO-d_6): δ_c 158.5 (C-4), 157.3 (C-2), 152.9 (C-8*a*), 144.6 (C-6), 138.7 (C-1′), 130.7 (C-3′), 130.3 (C-5′), 129.6 (C-8), 126.7 (C-7), 125.7 (C-4′), 123.5 (C-2′), 122.2 (C-6′), 120.7 (C-5), 114.4 (C-4*a*); IR (KBr, cm^{-1}): 3400 (N–H), 1610 (C=N), 1526 (N=O), 1113 (C–Cl); EI-MS: *m/z* (rel. abund. %), 338 [M^++4] (10), 336 [M^++2] (55), 334 $[M]^+$ (90), 333 (100), 289 (34), 287 (52), 253 (16); HREI-MS: *m/z* calcd for $C_{14}H_8Cl_2N_4O_2$ $[M]^+$ 334.0024; Found 334.0013; Anal. Calcd for $C_{14}H_8Cl_2N_4O_2$: C, 50.17; H, 2.41; Cl, 21.16; N, 16.72; O, 9.55; Found: C, 50.19; H, 2.39; N, 16.74.

4.3.18. 4-(2′,5′-Dimethoxyphenyl)amino-6-nitroquinazoline (18)

Yield: 54%; m.p. 170-172 °C; R_f: 0.11 (ethyl acetate/hexanes, 3:7); ^{1}H-NMR: (300 MHz, DMSO-d_6): δ_H 10.22 (s, 1H, NH), 9.58 (d, 1H, $J_{5,7}$ = 1.8 Hz, H-5), 8.56 (m, 2H, H-7, H-2), 7.91 (d, 1H, $J_{8,7}$ = 9.3 Hz, H-8), 7.09 (d, 1H, $J_{6',4'}$ = 1.8 Hz, H-6′), 7.05 (s, 1H, H-3′), 6.89 (dd, 1H, $J_{4',3'}$ = 8.7 Hz, $J_{4',6'}$ = 2.7 Hz, H-4′), 3.72 (s, 3H, 5′-OCH_3), 3.71 (s, 3H, 2′-OCH_3); ^{13}C-NMR: (100 MHz, DMSO-d_6): δ_c 159.9 (C-4), 157.9 (C-2), 152.9 (C-8*a*), 152.1 (C-5′), 148.1 (C-2′), 144.3 (C-6), 138.7 (C-1′), 129.2 (C-8), 126.9 (C-4*a*), 126.4 (C-7), 120.9 (C-5), 114.0 (C-3′), 112.8 (C-4′), 111.8 (C-6′), 56.0 (5′-OCH_3), 55.4 (2′-OCH_3); IR (KBr, cm^{-1}): 3420 (N–H), 1618 (C=N), 1539 (N=O), 1263 (C–O); EI-MS: *m/z* (rel. abund. %), 326 $[M]^+$ (16), 311 (3), 295 (100), 249 (36); HREI-MS: *m/z* calcd for $C_{16}H_{14}N_4O_4$ $[M]^+$ 326.1015; Found 326.1044; Anal. Calcd for $C_{16}H_{14}N_4O_4$: C, 58.89; H, 4.32; N, 17.17; O, 19.61; Found: C, 58.87; H, 4.30; N, 17.18.

4.3.19. 4-Phenylamino-6-nitroquinazoline (19)

Yield: 82%; m.p. 241-242 °C (lit. 242-243 °C [44]); R_f: 0.34 (ethyl acetate/hexanes, 3:7); ^{1}H-NMR: (300 MHz, DMSO-d_6): δ_H 10.45 (s, 1H, NH), 9.67 (d, 1H, $J_{5,7}$ = 2.1 Hz, H-5), 8.70 (s, 1H, H-2), 8.57 (dd, 1H, $J_{7,8}$ = 9.0 Hz, $J_{7,5}$ = 2.1 Hz, H-7), 7.94 (d, 1H, $J_{8,7}$ = 9.0 Hz, H-8), 7.84 (d, 2H, $J_{2',3'}$ = $J_{6',5'}$ = 7.8 Hz, H-2′, H-6′), 7.45 (d, 2H, $J_{3',2'}$ = $J_{5',6'}$ = 7.8 Hz, H-3′, H-5′), 7.21 (t, 1H, $J_{4'(3',2')}$ = $J_{4'(5',6')}$ = 7.5 Hz, H-4′); ^{13}C-NMR: (100 MHz, DMSO-d_6): δ_c 158.7 (C-4), 157.6 (C-2), 153.0 (C-8*a*), 144.4 (C-6), 138.3 (C-1′), 129.4 (C-8), 128.4 (C-3′, C-5′), 126.5 (C-7), 124.5 (C-4′), 122.9 (C-2′, C-6′), 120.8 (C-5), 114.3 (C-4*a*); IR (KBr, cm^{-1}): 3279 (N–H), 1624 (C=N), 1531 (N=O); EI-MS: *m/z* (rel. abund. %), 266 $[M]^+$ (90), 265 (100), 219 (100), 77 (12); HREI-MS: *m/z* calcd for $C_{14}H_{10}N_4O_2$ $[M]^+$ 266.0804; Found 266.0792; Anal. Calcd for $C_{14}H_{10}N_4O_2$: C, 63.15; H, 3.79; N, 21.04; O, 12.02; Found: C, 63.13; H, 3.81; N, 21.05.

4.3.20. 4-(4′-Ethylphenyl)amino-6-nitroquinazoline (20)

Yield: 75%; m.p. 195 °C; R_f: 0.42 (ethyl acetate/hexanes, 3:7); ^{1}H-NMR: (300 MHz, DMSO-d_6): δ_H 10.41 (s, 1H, NH), 9.65 (d, 1H, $J_{5,7}$ = 2.1 Hz, H-5), 8.66 (s, 1H, H-2), 8.56 (dd, 1H, $J_{7,8}$ = 9.0 Hz, $J_{7,5}$ = 2.1 Hz, H-7), 7.93 (d, 1H, $J_{8,7}$ = 9.3 Hz, H-8), 7.72 (d, 2H, $J_{2',3'}$ = $J_{6',5'}$ = 8.4 Hz, H-2′, H-6′), 7.27 (d, 2H, $J_{3',2'}$ = $J_{5',6'}$ = 8.4 Hz, H-3′, H-5′), 2.63 (q, 2H, J = 15.3 Hz, 7.5 Hz, CH_2), 1.22 (t, 3H, J = 7.5 Hz, CH_3); ^{13}C-NMR: (150 MHz, DMSO-d_6): δ_c 158.8 (C-4), 157.8 (C-2), 153.1 (C-8*a*), 144.4 (C-6), 140.1 (C-4′), 135.9 (C-1′), 129.4 (C-8), 127.8 (C-3′, C-5′), 126.5 (C-7), 123.1 (C-2′, C-6′), 120.8 (C-5), 114.3 (C-4*a*), 27.7 (4′-$\underline{C}H_2CH_3$), 15.7 (4′-$CH_2\underline{C}H_3$); IR (KBr, cm^{-1}): 3400 (N–H), 1620 (C=N), 1537 (N=O); EI-MS: *m/z* (rel. abund.

%), 294 $[M]^+$ (100), 293 (96), 279 (56), 263 (11), 247 (27), 233 (29); HREI-MS: *m/z* calcd for $C_{16}H_{14}N_4O_2$ $[M]^+$ 294.1117; Found 294.1095; Anal. Calcd for $C_{16}H_{14}N_4O_2$: C, 65.30; H, 4.79; N, 19.04; O, 10.87; Found: C, 65.28; H, 4.78; N, 19.06.

4.3.21. 4-[4′-(Methylsulfanyl)phenyl]amino-6-nitroquinazoline (21)

Yield: 86%; m.p. 203-205 °C; R_f: 0.31 (ethyl acetate/hexanes, 3:7); ^{1}H-NMR: (300 MHz, DMSO-d_6): δ_H 10.44 (s, 1H, NH), 9.65 (d, 1H, $J_{5,7}$ = 2.1 Hz, H-5), 8.69 (s, 1H, H-2), 8.56 (dd, 1H, $J_{7,8}$ = 9.3 Hz, $J_{7,5}$ = 2.1 Hz, H-7), 7.93 (d, 1H, $J_{8,7}$ = 9.3 Hz, H-8), 7.81 (d, 2H, $J_{2',3'}$ = $J_{6',5'}$ = 8.7 Hz, H-2′, H-6′), 7.34 (d, 2H, $J_{3',2'}$ = $J_{5',6'}$ = 8.7 Hz, H-3′, H-5′), 3.30 (s, 3H, 4′-SCH_3); ^{13}C-NMR: (100 MHz, DMSO-d_6): δ_c 158.6 (C-4), 157.6 (C-2), 153.0 (C-8*a*), 144.4 (C-6), 135.6 (C-1′), 133.5 (C-4′), 129.3 (C-8), 126.5 (C-7), 126.4 (C-3′, C-5′), 123.4 (C-2′, C-6′), 120.7 (C-5), 114.3 (C-4*a*), 15.2 (4′-SCH_3); IR (KBr, cm^{-1}): 3628 (N–H), 1589 (C=N), 1526 (N=O), 1121 (C–S); EI-MS: *m/z* (rel. abund. %), 312 $[M]^+$ (100), 311 (40), 297 (10), 265 (16); HREI-MS: *m/z* calcd for $C_{15}H_{12}N_4O_2S$ $[M]^+$ 312.0681; Found 312.0687; Anal. Calcd for $C_{15}H_{12}N_4O_2S$: C, 57.68; H, 3.87; N, 17.94; O, 10.24; S, 10.27; Found: C, 57.70; H, 3.89; N, 17.92.

4.3.22. 4-(5′-Chloro-2′-methylphenyl)amino-6-nitroquinazoline (22)

Yield: 42%; m.p. 184-185 °C; R_f: 0.38 (ethyl acetate/hexanes, 3:7); ^{1}H-NMR: (300 MHz, DMSO-d_6): δ_H 10.42 (s, 1H, NH), 9.55 (s, 1H, H-5), 8.56 (m, 2H, H-7, H-2), 7.93 (d, 1H, $J_{8,7}$ = 9.0 Hz, H-8), 7.43 (s, 1H, H-6′), 7.37 (d, 1H, $J_{3',4'}$ = 8.1 Hz, H-3′), 7.31 (d, 1H, $J_{4',3'}$ = 7.8 Hz, H-4′), 2.17 (s, 3H, 2′-CH_3); ^{13}C-NMR: (75 MHz, DMSO-d_6): δ_c 158.9 (C-4), 157.8 (C-2), 153.0 (C-8*a*), 144.4 (C-6), 136.2 (C-1′), 132.0 (C-5′), 130.0 (C-3′), 129.3 (C-8), 127.1 (C-2′), 126.6 (C-7), 126.5 (C-4′), 122.8 (C-6′), 120.9 (C-5), 114.3 (C-4*a*), 17.4 (2′-CH_3); IR (KBr, cm^{-1}): 3481 (N–H), 1620 (C=N), 1528 (N=O), 1111 (C–Cl); EI-MS: *m/z* (rel. abund. %), 316 $[M^+{+}2]$ (36), 314 $[M]^+$ (100), 299 (94), 267 (42), 253 (52); HREI-MS: *m/z* calcd for $C_{15}H_{11}ClN_4O_2$ $[M]^+$ 314.0571; Found 314.0549; Anal. Calcd for $C_{15}H_{11}ClN_4O_2$: C, 57.24; H, 3.52; Cl, 11.26; N, 17.80; O, 10.17; Found: C, 57.22; H, 3.54; N, 17.82.

4.3.23. 4-(2′,5′-Dichlorophenyl)amino-6-nitroquinazoline (23)

Yield: 45%; m.p. 222-224 °C; R_f: 0.50 (ethyl acetate/hexanes, 3:7); ^{1}H-NMR: (300 MHz, DMSO-d_6): δ_H 10.67 (s, 1H, NH), 9.57 (s, 1H, H-5), 8.63 (m, 2H, H-7,8), 7.98 (s, 1H, H-2), 7.74 (m, 2H, H-3′, H-4′), 7.44 (s, 1H, H-6′); ^{13}C-NMR: (150 MHz, DMSO-d_6): δ_c 158.6 (C-4), 157.7 (C-2), 152.8 (C-8*a*), 144.6 (C-6), 136.7 (C-1′), 135.4 (C-5′), 132.3 (C-3′), 130.4 (C-2′),

129.2 (C-8), 128.2 (C-4′), 126.9 (C-7), 122.8 (C-6′), 120.9 (C-5), 114.1 (C-4*a*); IR (KBr, cm^{-1}): 3410 (N–H), 1616 (C=N), 1533 (N=O), 1120 (C–Cl); EI-MS: *m/z* (rel. abund. %), 336 $[M^{+}+2]$ (5), 334 $[M]^{+}$ (7), 299 (100), 287 (5), 253 (62); HREI-MS: *m/z* calcd for $C_{14}H_8Cl_2N_4O_2$ $[M]^{+}$ 334.0024; Found 334.0034; Anal. Calcd for $C_{14}H_8Cl_2N_4O_2$: C, 50.17; H, 2.41; Cl, 21.16; N, 16.72; O, 9.55; Found: C, 50.19; H, 2.40; N, 16.71.

4.3.24. 4-(3′,4′-Dimethylphenyl)amino-6-nitroquinazoline (24)

Yield: 88%; m.p. 232-233 °C; R_f: 0.46 (ethyl acetate/hexanes, 3:7); ^{1}H-NMR: (300 MHz, DMSO-d_6): δ_H 10.34 (s, 1H, NH), 9.65 (d, 1H, $J_{5,7}$ = 2.1 Hz, H-5), 8.66 (s, 1H, H-2), 8.54 (dd, 1H, $J_{7,8}$ = 9.3 Hz, $J_{7,5}$ = 2.1 Hz, H-7), 7.91 (d, 1H, $J_{8,7}$ = 9.3 Hz, H-8), 7.56 (m, 2H, H-6′, H-2′), 7.18 (d, 1H, $J_{5',6'}$ = 8.7 Hz, H-5′), 2.25 (s, 3H, 3′-CH_3), 2.22 (s, 3H, 4′-CH_3); ^{13}C-NMR: (100 MHz, DMSO-d_6): δ_c 158.8 (C-4), 157.8 (C-2), 153.1 (C-8*a*), 144.4 (C-6), 136.2 (C-1′), 135.9 (C-3′), 132.6 (C-4′), 129.4 (C-8), 129.0 (C-5′), 126.4 (C-7), 124.1 (C-6′), 120.8 (C-5), 120.5 (C-2′), 114.3 (C-4*a*), 19.5 (C-3′), 18.8 (C-4′); IR (KBr, cm^{-1}): 3277 (N–H), 1626 (C=N), 1528 (N=O); EI-MS: *m/z* (rel. abund. %), 294 $[M]^{+}$ (85), 293 (100), 279 (2), 263 (18), 247 (50), 120 (5); HREI-MS: *m/z* calcd for $C_{16}H_{14}N_4O_2$ $[M]^{+}$ 294.1117; Found 294.1137; Anal. Calcd for $C_{16}H_{14}N_4O_2$: C, 65.30; H, 4.79; N, 19.04; O, 10.87; Found: C, 65.33; H, 4.81; N, 19.02.

4.3.25. 4-(3′-Hydroxyphenyl)amino-6-nitroquinazoline (25)

Yield: 91%; m.p. 307-308 °C (lit. 306-308 °C [41]); R_f: 0.16 (ethyl acetate/hexanes, 3:7); ^{1}H-NMR: (300 MHz, DMSO-d_6): δ_H 10.32 (s, 1H, NH), 9.67 (d, 1H, $J_{5,7}$ = 2.1 Hz, H-5), 9.51 (s, 1H, 3′-OH), 8.70 (s, 1H, H-2), 8.56 (dd, 1H, $J_{7,8}$ = 9.0 Hz, $J_{7,5}$ = 2.1 Hz, H-7), 7.93 (d, 1H, $J_{8,7}$ = 9.0 Hz, H-8), 7.36 (s, 1H, H-2′), 7.26 (d, 1H, $J_{6',5'}$ = 8.1 Hz, H-6′), 7.21 (t, 1H, $J_{5'(4',6')}$ = 7.8 Hz, H-5′), 6.60 (d, 1H, $J_{4',5'}$ = 7.5 Hz, H-4′); ^{13}C-NMR: (100 MHz, DMSO-d_6): δ_c 158.8 (C-4), 157.7 (C-2), 157.4 (C-3′), 153.1 (C-8*a*), 144.5 (C-6), 139.3 (C-1′), 129.4 (C-8), 129.1 (C-5′), 126.5 (C-7), 120.9 (C-5), 114.4 (C-4*a*), 113.5 (C-6′), 111.7 (C-4′), 110.0 (C-2′); IR (KBr, cm^{-1}): 3483 (O–H), 3383 (N–H), 1618 (C=N), 1539 (N=O), 1254 (C–O); EI-MS: *m/z* (rel. abund. %), 282 $[M]^{+}$ (57), 281 (100), 265 (2), 250 (16), 235 (64); HREI-MS: *m/z* calcd for $C_{14}H_{10}N_4O_3$ $[M]^{+}$ 282.0753; Found 282.0757; Anal. Calcd for $C_{14}H_{10}N_4O_3$: C, 59.57; H, 3.57; N, 19.85; O, 17.01; Found: C, 59.59; H, 3.59; N, 19.84.

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Highlights:

Synthesis of twenty-four different derivatives of 4-Arylamino-6-nitroquinazolines

In vitro antileishmanial potential assesment

Discovery of a novel class of antileshmanial compounds