Synthesis of substituted isoindolo[2,1-*a*]quinoxalin-6-yl–amino and 6-imino-5-yl thiourea derivatives

Barbara Parrino, Cristina Ciancimino, Chandrakant Sarwade, Virginia Spanò, Alessandra Montalbano, Paola Barraja, Girolamo Cirrincione, Patrizia Diana, and Anna Carbone*

Dipartimento di Scienze e Tecnologie Biologiche Chimiche e Farmaceutiche, Università degli Studi di Palermo, Via Archirafi 32, 90123 Palermo, Italy
E-mail: anna.carbone@unipa.it

DOI: http://dx.doi.org/10.3998/ark.5550190.p008.858

Abstract

A series of substituted 1-(5-bromopyridin-2-yl)-3-[2-(isoindolo[2,1-*a*]quinoxalin-6-ylamino)ethyl]thiourea and 1-(5-bromopyridin-2-yl)-3-[2-(6-iminoisoindolo[2,1-*a*]quinoxalin-5(6*H*)-yl)ethyl]thiourea derivatives were prepared in good yields (63-85%) by reaction between the corresponding amino compounds with 5-bromo-2-isothiocyanatopyridine. All thiourea derivatives, tested for inhibition of HIV-1 RT, showed no significant antiviral activity.

Keywords: AIDS, NNRTIs, isoindolo-quinoxalines, quinoxalinylethylpyridylthioureas, antiviral activity

Introduction

Human immunodeficiency virus (HIV) is a retrovirus responsible for transmission and development of the acquired immune deficiency syndrome (AIDS). It is characterized by the presence of a viral reverse transcriptase (RT) that is able to synthesize DNA from the viral RNA genoma. Due to its important role in the viral life cycle, this enzyme is considered an excellent target in the chemotherapy against AIDS. In the current treatment strategy, called highly active antiretroviral therapy (HAART), HIV-1 RT inhibitors are used in combination with HIV-1 protease inhibitors.[1-3]

There are two classes of HIV-1 RT inhibitors: nucleoside analogues (NRTIs), for example AZT, ddI, ddC, d4T and non-nucleoside analogues (NNRTIs), for example nevirapine, efavirenz, delarvidine. NRTIs are competitive inhibitors that act at the catalytic site of the enzyme by interrupting DNA synthesis.[4] NNRTIs are non-competitive inhibitors, structurally diverse, that bind to a hydrophobic pocket located approximately 10 Å away from the catalytic

site. Their binding leads to a distorsion of the catalytic pocket preventing the enzyme to carry out its normal functions.[5,6]

Most NNRTIs are highly specific against HIV-1 RT and have a low toxicity for the human cells but show a reduced efficacy against mutated variants of RT.[7,8]
For this reason in the last years many efforts have been done to find new NNRTIs able to inhibit both wild-type and mutants HIV-1 RT that are resistant to the common antiretroviral drugs.[9,10]

The quinoxaline ring and structurally related quinoxalinone constitute the skeleton of many compounds showing a variety of biological activities.[11] Some quinoxaline derivatives (for example S-2720,[12] HBY097[13] and GW420867X[14]) have been reported as excellent NNRTIs and in particular HBY 097 and GW420867X were also selected for clinical trials. They were highly potent inhibitors of HIV-1 replication in different human cell lines showing IC_{50} values in the low nanomolar range. The compounds were also active against various HIV-1 subtypes and mutant reverse transcriptases. Compounds with a heteroarylsulfonylquinoxaline structure were also reported for their properties to inhibit the RT with IC_{50} at submicromolar range (Figure 1).[15]

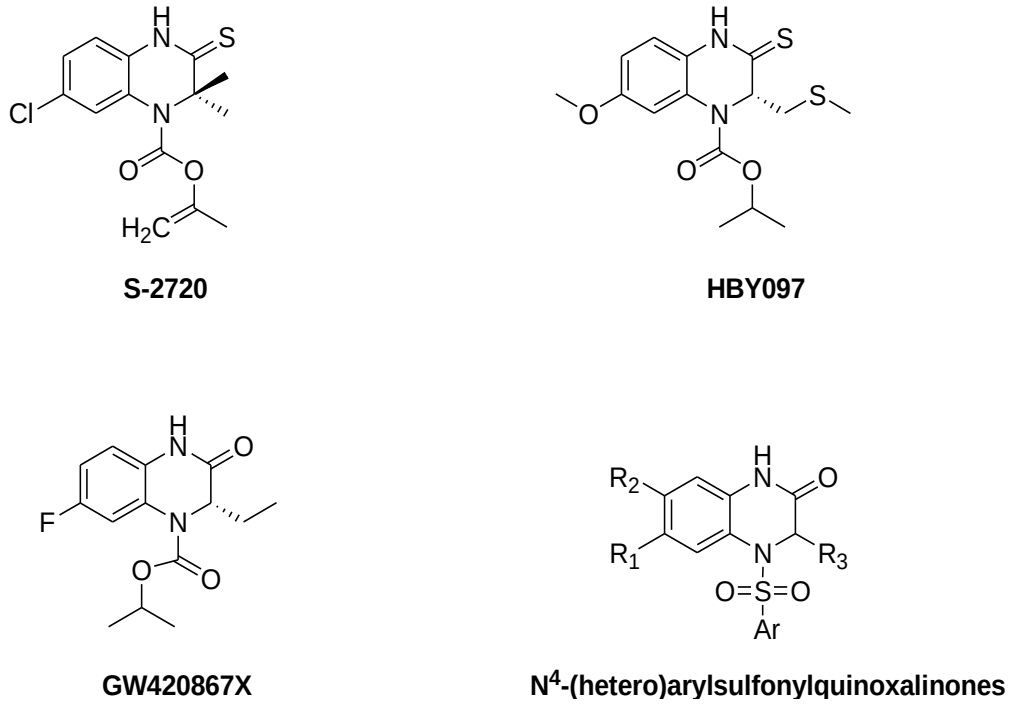


Figure 1. NNRTIs having a quinoxaline skeleton.

Quinoxalinylethylpyridylthioureas (QXPTs) of type **1** and **2** (Figure 2) represent another class of NNRTIs; many compounds showed a potent activity against both HIV-1 wild-type RT and various HIV-1 mutants HIV-1 RT.[16] Considering the good experience reached in the course of our researches on polycyclic nitrogen systems, bearing pyrrole,[17-24] indole,[25-35] isoindole[36-38]and indazole[39] moieties, we have decided to synthesize the QXPT analogues of type **3** and **4** bearing an isoindole moiety instead of the five-membered heterocyclic ring. Moreover the replacement

of the oxygen atom with a nitrogen atom could have increased the pharmacokinetic profile (Figure 2).

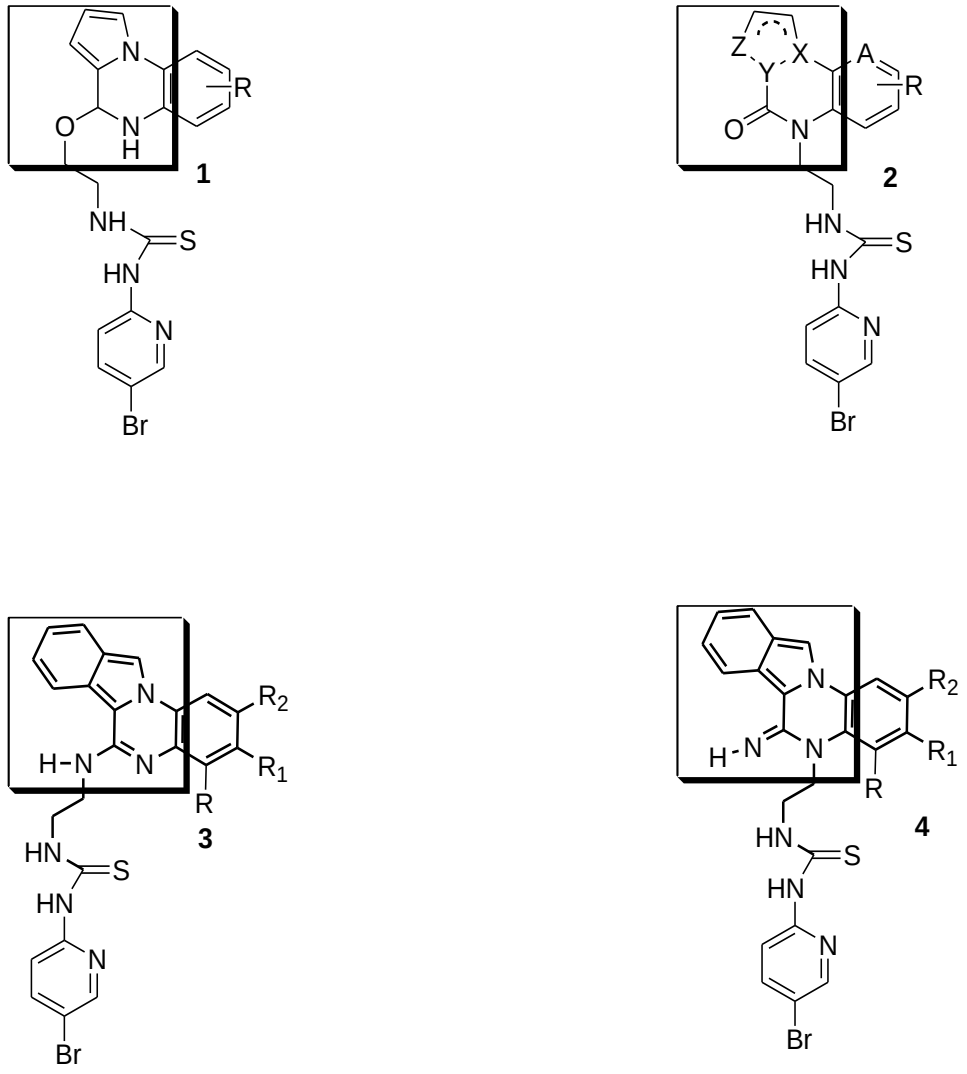


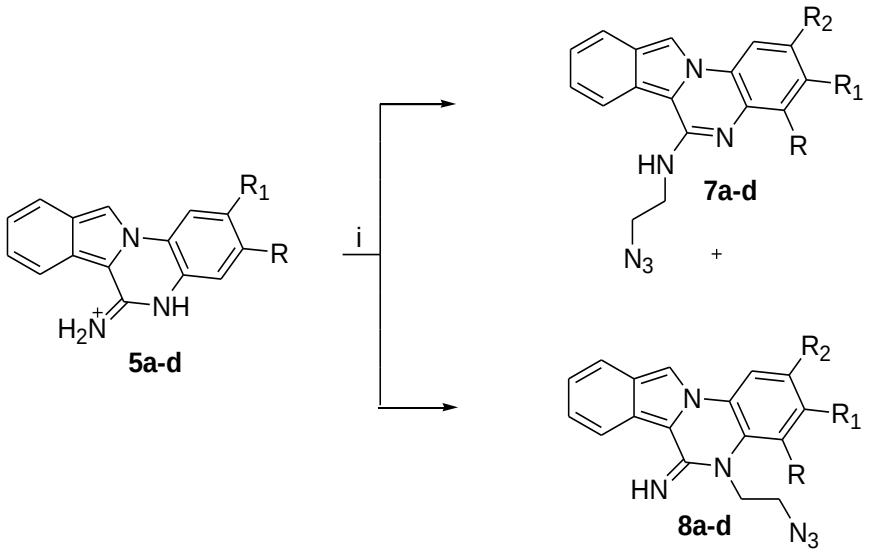
Figure 2. Quinoxalinylethylpyridylthioureas **1-4**.

Results and Discussion

The key intermediates for the synthesis of 1-(5-bromopyridin-2-yl)-3-[2-(isoindolo[2,1-*a*]-quinoxalin-6-ylamino)ethyl]thiourea **3a-d** and 1-(5-bromopyridin-2-yl)-3-[2-(6-iminoisoindolo-[2,1-*a*]quinoxalin-5(6*H*)-yl)ethyl]thiourea derivatives **4a-d** were the isoindolo[2,1-*a*]quinoxalin-6(5*H*)-imine acetates **5a-d** prepared by us as previously reported[38] (Scheme 1).

The reaction of the latter compounds with 2-azidoethyl-4-methylbenzenesulfonate **6**, properly prepared from 2-chloroethanol with sodium azide and subsequent tosylation of the

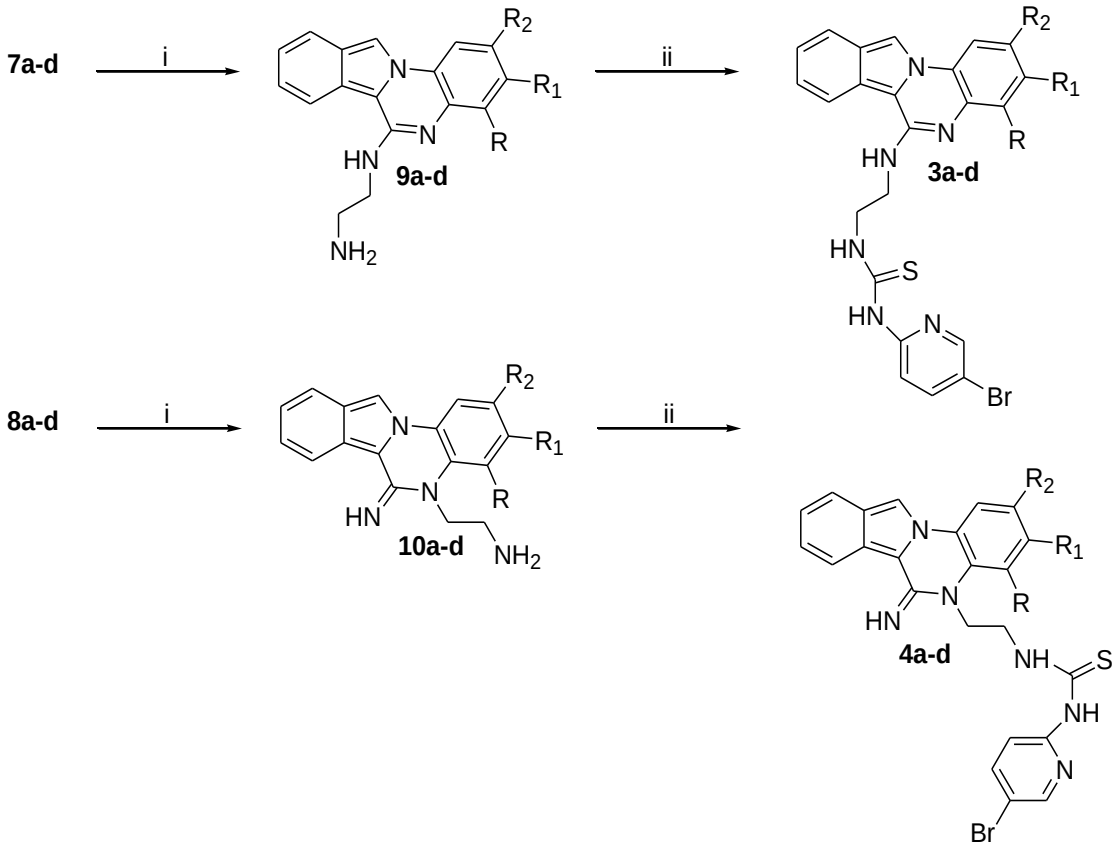
alcohol group,[40] in dimethylformamide and in the presence of potassium carbonate as base, furnished both *N*-(2-azidoethyl)isoindolo[2,1-*a*]quinoxalin-6-amines **8a-d** (40-45%) and 5-(2-azidoethyl)isoindolo[2,1-*a*]quinoxalin-6(5*H*)-imines **9a-d** (46-51%) separated by column chromatography (Scheme 1).



a) R = R_1 = R_2 = H; b) R = R_2 = H, R_1 = OMe; c) R = H, R_1 = R_2 = Cl; d) R = Me, R_1 = R_2 = H

Scheme 1. *Reagents and conditions*: (i) K_2CO_3, DMF, 2 h, rt, then 2-azidoethyl-4-methylbenzenesulfonate **6**, 12 h, 90 °C.

The azidoethylquinoxalines **7a-d** and **8a-d** obtained were reduced to the corresponding amino compounds[16] **9a-d** and **10a-d** in good yields (58-64% and 62-78% respectively) using propane-1,3-dithiol and triethylamine (TEA) (Scheme 2). The subsequent functionalization of the obtained amino derivatives gave the desired 1-(5-bromopyridin-2-yl)-3-[2-(isoindolo[2,1-*a*]quinoxalin-6-ylamino)ethyl]thiourea **3a-d** (63-85%) and 1-(5-bromopyridin-2-yl)-3-[2-(6-iminoisoindolo[2,1-*a*]quinoxalin-5(6*H*)-yl)ethyl]thiourea **4a-d** (67-81%) derivatives by a coupling reaction in dimethylformamide with 5-bromo-2-isothiocyanatopyridine obtained from a reaction between 2-amino-5-bromopyridine and thiocarbonyldiimidazole in chloroform[41] (Scheme 2).



a) R = R_1 = R_2 = H; b) R = R_2 = H, R_1 = OMe; c) R = H, R_1 = R_2 = Cl; d) R = Me, R_1 = R_2 = H

Scheme 2. *Reagents and conditions*: (i) TEA, propane-1,3-dithiol, MeOH, 24 h, rt; (ii) 5-bromo-2-isothiocyanatopyridine, DMF, 16 h, 100 °C.

Furthermore, the antiviral activity of compounds **3** and **4** was assayed. In particular, their capacity to inhibit the activity of HIV-1 RT, was evaluated. Unfortunately, none of the derivatives **3** and **4** showed inhibition up to a concentration of 100 μM.

Experimental Section

General. All melting points were taken on a Büchi-Tottoly capillary apparatus and are uncorrected. IR spectra were determined in bromoform with a Shimadzu FT/IR 8400S spectrophotometer. ^{1}H and ^{13}C NMR spectra were measured at 200 and 50.0 MHz, respectively, in DMSO-d_6 or $CDCl_3$ solution, using a Bruker Avance II series 200 MHz spectrometer. Column chromatography was performed with Merk silica gel 230−400 mesh ASTM or with Büchi Sepacor chromatography module (prepacked cartridge system). Elemental analyses (C, H, N) were within ±0.4% of theoretical values and were performed with a VARIO EL III elemental analyzer.

General procedure for the preparation of substituted *N*-(2-azidoethyl)isoindolo[2,1-*a*]quinoxalin-6-amines (8a-d) and 5-(2-azidoethyl)isoindolo[2,1-*a*]quinoxalin-6(5*H*)-imines (9a-d). To a solution of isoindolo[2,1-*a*]quinoxalin-6(5*H*)-imine acetates **5a-d**[38] (2.10 mmol) in DMF (7 mL), potassium carbonate (7.40 mmol, 1.05 g) was added and the reaction mixture was stirred for 2 hours at room temperature. Then 2-azidoethyl-4-methylbenzenesulfonate **6**[40] (6.40 mmol, 1.50 g) was added and the mixture was heated at 90 °C for 12 hours. Water was added and the resulted solution was extracted with ethyl acetate (3 x 60 mL), dried (Na_2SO_4) and evaporated under reduced pressure. The obtained residue was purified by column chromatography to give corresponding derivatives **7a-d** and **8a-d**.

***N*-(2-Azidoethyl)isoindolo[2,1-*a*]quinoxalin-6-amine (7a).** The residue was purified by chromatography eluting with DCM. White solid; yield: 45%; mp 156 °C; IR ($CHBr_3$) ν 3429 (NH), 2257 (N_3) cm^{-1}; ^{1}H NMR (200 MHz, DMSO-d_6) δ 3.74-3.80 (m, 2H, CH_2), 4.80 (t, *J* 5.9 Hz, 2H, CH_2), 7.45 (d, *J* 8.0 Hz, 1H, Ar-H), 7.63 (d, *J* 8.0 Hz, 1H, Ar-H), 7.79-8.08 (m, 4H, Ar-H), 8.22 (d, *J* 7.5 Hz, 1H, Ar-H), 8.41 (d, *J* 7.7 Hz, 1H, Ar-H), 8.89 (d, *J* 7.7 Hz, 1H, Ar-H), 11.20 (br, 1H, NH); ^{13}C NMR (50 MHz, DMSO-d_6) δ 39.6 (CH_2), 48.1 (CH_2), 127.1 (C), 127.5 (CH), 127.6 (CH), 128.1 (CH), 128.6 (CH), 128.8 (CH), 129.8 (CH), 131.2 (CH), 131.7 (CH), 132.4 (C), 133.7 (CH), 138.5 (C), 140.2 (C), 143.4 (C), 161.2 (C). Anal. Calcd for $C_{17}H_{14}N_6$: C, 67.54; H, 4.67; N, 27.80. Found: C, 67.38; H, 4.89; N, 27.64.

Further elution with DCM/Ethyl acetate 8/2 gave **5-(2-azidoethyl)isoindolo[2,1-*a*]quinoxalin-6(5*H*)-imines (8a).** White solid; yield: 50%; mp 165 °C; IR ($CHBr_3$) ν 3407 (NH), 2256 (N_3) 1711 (C=NH) cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 3.83 (t, *J* 4.9 Hz, 2H, CH_2), 5.05 (t, *J* 4.9 Hz, 2H, CH_2), 7.80-7.93 (m, 4H, Ar-H), 8.01 (td, *J* 1.3, 7.2 Hz, 1H, Ar-H), 8.28-8.35 (m, 2H, Ar-H), 8.43 (dd, *J* 0.8, 7.9 Hz, 1H, Ar-H), 9.26 (dd, *J* 0.8, 7.9 Hz, 1H, Ar-H), 11.36 (br, 1H, NH); ^{13}C NMR (50 MHz, $CDCl_3$) δ 50.2 (CH_2), 66.5 (CH_2), 121.01 (C), 122.7 (C), 124.8 (CH), 125.4 (CH), 129.2 (CH), 129.3 (CH), 129.4 (CH), 130.5 (CH), 130.8 (CH), 132.5 (CH), 134.9 (C), 137.6 (C), 140.8 (CH), 141.3 (C), 143.3 (C). Anal. Calcd for $C_{17}H_{14}N_6$: C, 67.54; H, 4.67; N, 27.80. Found: C, 67.76; H, 4.32; N, 27.92.

***N*-(2-Azidoethyl)-3-methoxyisoindolo[2,1-*a*]quinoxalin-6-amine (7b).** The residue was purified by chromatography eluting with DCM/Ethyl acetate 9/1. White solid; yield: 43%; mp 189 °C; IR ($CHBr_3$) ν 3480 (NH), 2256 (N_3) cm^{-1}; ^{1}H NMR (200 MHz, DMSO-d_6) δ 3.75-3.81 (m, 2H, CH_2), 3.99 (s, 3H, OCH_3), 4.79 (t, *J* 6.0 Hz, 2H, CH_2), 7.40-7.50 (m, 2H, Ar-H), 7.82-8.08 (m, 4H, Ar-H), 8.39 (dd, *J* 0.9, 7.1 Hz, 1H, Ar-H), 8.84 (dd, *J* 0.9, 7.1 Hz, 1H, Ar-H), 11.18 (br, 1H, NH); ^{13}C NMR (50 MHz, DMSO-d_6) δ 39.5 (CH_2), 48.1 (CH_2), 56.0 (CH_3), 105.7 (CH), 121.7 (CH), 123.6 (CH), 126.5 (C), 128.0 (CH), 130.0 (CH), 130.9 (CH), 132.6 (C), 132.7 (C), 133.6 (CH), 134.6 (C), 139.9 (CH), 142.3 (C), 161.3 (C), 161.5 (C). Anal. Calcd for $C_{18}H_{16}N_6O$: C, 65.05; H, 4.85; N, 25.29. Found: C, 64.81; H, 4.69; N, 25.50.

Further elution with DCM/Ethyl acetate 8/2 gave **5-(2-azidoethyl)-3-methoxyisoindolo[2,1-*a*]quinoxalin-6(5*H*)-imine (8b).** White solid; yield: 46%; mp 189 °C; IR ($CHBr_3$) ν 3021 (NH), 2104 (N_3), 1695 (C=NH) cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 3.83 (t, *J* 6.0 Hz, 2H, CH_2), 4.02 (s, 3H, OCH_3), 5.08 (t, *J* 6.0 Hz, 2H, CH_2), 7.46-7.55 (m, 2H, 2 x Ar-H), 7.80-8.02 (m, 3H, 3 x

Ar-H), 8.18 (d, *J* 9.1 Hz, 1H, Ar-H), 8.41 (d, *J* 8.0 Hz, 1H, Ar-H), 9.19 (d, *J* 8.0 Hz, 1H, Ar-H), 11.34 (br, 1H, NH); ^{13}C NMR (50 MHz, $CDCl_3$) δ 29.7 (CH_2), 50.2 (CH_2), 55.8 (CH_3), 105.6 (CH), 122.1 (C), 123.8 (CH), 124.2 (CH), 124.5 (C), 125.3 (CH), 129.0 (CH), 130.1 (CH), 130.3 (CH), 132.4 (CH), 135.0 (C), 135.4 (C), 137.9 (C), 145.1 (C), 161.4 (C). Anal. Calcd for $C_{18}H_{16}N_6O$: C, 65.05; H, 4.85; N, 25.29. Found: C, 64.75; H, 5.12; N, 25.41.

***N*-(2-Azidoethyl)-2,3-dichloroisoindolo[2,1-*a*]quinoxalin-6-amine (7c).** The residue was purified by chromatography eluting with DCM/Ethyl acetate 9/1. White solid; yield: 40%; mp 152 °C; IR ($CHBr_3$) ν 3429 (NH), 2256 (N_3) cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 3.73-3.80 (m, 2H, CH_2), 4.92 (t, *J* 6.3 Hz, 2H, CH_2), 7.83-7.93 (m, 3H, Ar-H), 8.21 (s, 1H, Ar-H), 8.33 (s, 1H, Ar-H), 8.52 (d, *J* 7.7 Hz, 1H, Ar-H), 8.95 (d, *J* 7.7 Hz, 1H, Ar-H), 11.19 (br, 1H, NH); ^{13}C NMR (50 MHz, $CDCl_3$) δ 39.9 (CH_2), 47.6 (CH_2), 124.8 (CH), 125.1 (C), 127.5 (C), 128.6 (CH), 128.8 (CH), 129.6 (CH), 131.8 (CH), 131.9 (CH), 132.4 (C), 133.7 (CH), 135.5 (C), 139.5 (C), 139.7 (C), 158.6 (C), 161.9 (C). Anal. Calcd for $C_{17}H_{12}Cl_2N_6$: C, 55.00; H, 3.26; N, 22.64. Found: C, 54.79; H, 3.42; N, 22.43.

Further elution with DCM/Ethyl acetate 8/2 gave **5-(2-azidoethyl)-2,3-dichloroisoindolo[2,1-*a*]quinoxalin-6(5*H*)-imine (8c).** White solid; yield: 51%; mp 169 °C; IR ($CHBr_3$) ν 3409 (NH), 2105 (N_3), 1722 (C=NH) cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 3.83 (t, *J* 4.9 Hz, 2H, CH_2), 5.03 (t, *J* 4.9 Hz, 2H, CH_2), 7.83-8.06 (m, 3H, Ar-H), 8.36-8.43 (m, 3H, Ar-H), 9.18 (dd, *J* 1.2, 8.0 Hz, 1H, Ar-H), 11.35 (br, 1H, NH); ^{13}C NMR (50 MHz, $CDCl_3$) δ 50.1 (CH_2), 66.7 (CH_2), 122.8 (CH), 124.9 (CH), 125.5 (CH), 129.4 (CH), 129.6 (CH), 131.4 (CH), 132.8 (CH), 133.9 (C), 134.5 (C), 135.2 (C), 138.5 (C), 139.7 (C), 141.8 (C), 148.0 (C), 163.5 (C). Anal. Calcd for $C_{17}H_{12}Cl_2N_6$: C, 55.00; H, 3.26; N, 22.64. Found: C, 55.32; H, 3.48; N, 22.42.

***N*-(2-Azidoethyl)-2-methylisoindolo[2,1-*a*]quinoxalin-6-amine (7d).** The residue was purified by chromatography eluting with DCM/Ethyl acetate 9/1. White solid; yield: 44%; mp 147 °C; IR ($CHBr_3$) ν 3391 (NH), 2257 (N_3) cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 2.80 (s, 3H, CH_3), 3.77-3.83 (m, 2H, CH_2), 4.95 (t, *J* 6.6 Hz, 2H, CH_2), 7.58-7.68 (m, 3H, Ar-H), 7.78 (td, *J* 1.4, 7.3 Hz, 1H, Ar-H), 7.90 (td, *J* 1.4, 7.3 Hz, 1H, Ar-H), 8.00-8.06 (m, 1H, Ar-H), 8.53 (dd, *J* 0.8, 7.9 Hz, 1H, Ar-H), 8.98 (dd, *J* 0.8, 7.9 Hz, 1H, Ar-H), 11.20 (br, 1H, NH); ^{13}C NMR (50 MHz, $CDCl_3$) δ 17.3 (CH_3), 40.0 (CH_2), 48.5 (CH_2), 124.5 (CH), 127.0 (CH), 127.4 (C), 128.1 (CH), 128.2 (CH), 128.6 (CH), 129.6 (C), 130.8 (CH), 131.2 (CH), 133.0 (C), 133.4 (CH), 136.2 (C), 139.6 (C), 139.9 (C), 162.2 (C). Anal. Calcd for $C_{18}H_{16}N_6$: C, 68.34; H, 5.10; N, 26.56. Found: C, 68.62; H, 4.86; N, 26.82.

Further elution with DCM/Ethyl acetate 8/2 gave **5-(2-azidoethyl)-2-methylisoindolo[2,1-*a*]quinoxalin-6(5*H*)-imine (8d).** Yellow solid; yield: 50%; mp 161 °C; IR ($CHBr_3$) ν 3442 (NH), 2256 (N_3), 1729 (C=NH) cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 2.98 (s, 3H, CH_3), 3.82 (t, *J* 4.9 Hz, 2H, CH_2), 5.08 (t, *J* 4.9 Hz, 2H, CH_2), 7.67-8.04 (m, 5H, Ar-H), 8.17 (dd, *J* 2.5, 7.5 Hz, 1H, Ar-H), 8.43 (dt, *J* 0.8, 8.0 Hz, 1H, Ar-H), 9.26 (dt, *J* 0.8, 8.0 Hz, 1H, Ar-H), 11.33 (br, 1H, NH); ^{13}C NMR (50 MHz, $CDCl_3$) δ 18.0 (CH_3), 50.3 (CH_2), 66.4 (CH_2), 122.6 (CH), 124.7 (CH), 125.3 (CH), 127.2 (CH), 129.1 (CH), 130.2 (CH), 130.6 (CH), 132.4 (CH), 135.1 (C), 137.1 (C),

137.4 (C) 141.4 (C), 142.6 (C), 146.7 (C), 162.7 (C). Anal. Calcd for $C_{18}H_{16}N_6$: C, 68.34; H, 5.10; N, 26.56. Found: C, 68.72; H, 5.02; N, 26.73.

General procedure for the preparation of substituted *N*-(isoindolo[2,1-*a*]quinoxalin-6-yl)ethane-1,2-diamines (9a-d) and 2-(6-iminoisoindolo[2,1-*a*]quinoxalin-5(6*H*)-yl)ethanamines (10a-d). To a mixture of propane-1,3-dithiol (0.90 mmol, 0.09 mL) and triethylamine (0.90 mmol, 0.13 mL) a solution of the proper *N*-(2-azidoethyl)isoindolo[2,1-*a*]quinoxalin-6-amine **7a-d** or 5-(2-azidoethyl)isoindolo[2,1-*a*]quinoxalin-6(5*H*)-imine **8a-d** (0.30 mmol) in anhydrous methanol (3 mL) was added under argon atmosphere. The reaction mixture was stirred at room temperature for 24 hours then the solvent was evaporated under reduced pressure and the obtained residue was purified by chromatography eluting with DCM/Ethyl acetate 8/2 to give derivatives **9a-d** and **10a-d**.

***N*-(Isoindolo[2,1-*a*]quinoxalin-6-yl)ethane-1,2-diamine (9a).** White solid; yield: 58%; mp 177 °C; IR ($CHBr_3$) ν 3688, 3557 (NH_2), 3370 (NH) cm^{-1}; ^1H NMR (200 MHz, DMSO-d_6) δ 3.73-3.79 (m, 2H, CH_2), 4.78 (t, *J* 6.2 Hz, 2H, CH_2), 7.77-8.07 (m, 6H, Ar-H), 8.20 (dd, *J* 1.3, 8.1 Hz, 1H, Ar-H), 8.39 (dd, *J* 1.3, 8.1 Hz, 1H, Ar-H), 8.86 (dd, *J* 1.0, 7.9 Hz, 1H, Ar-H), 11.23 (br, 1H, NH); ^{13}C NMR (50 MHz, DMSO-d_6) δ 39.6 (CH_2), 48.1 (CH_2), 124.1 (CH), 127.1 (C), 127.5 (CH), 127.6 (C), 128.1 (CH), 128.6 (CH), 128.8 (CH), 129.8 (CH), 131.2 (CH), 131.7 (CH), 132.4 (C), 133.8 (CH), 138.6 (C), 140.3 (C), 161.2 (C). Anal. Calcd for $C_{17}H_{16}N_4$: C, 73.89; H, 5.84; N, 20.27. Found: C, 74.15; H, 6.02; N, 20.53.

***N*-(3-Methoxyisoindolo[2,1-*a*]quinoxalin-6-yl)ethane-1,2-diamine (9b)**. White solid; yield: 60%; mp 192.4 °C; IR ($CHBr_3$) ν 3440, 3429 (NH_2), 3398 (NH) cm^{-1}; ^1H NMR (200 MHz, DMSO-d_6) δ 3.73-3.79 (m, 2H, CH_2), 3.97 (s, 3H, OCH_3), 4.75 (t, *J* 6.3 Hz, 2H, CH_2), 7.32 (d, *J* 2.8 Hz, 1H, Ar-H), 7.41 (dd, *J* 2.8, 9.1 Hz, 1H, Ar-H), 7.79-8.06 (m, 4H, Ar-H), 8.35 (dd, *J* 0.8, 7.5 Hz, 1H, Ar-H), 8.77 (dd, *J* 0.8, 7.5 Hz, 1H, Ar-H), 11.25 (br, 1H, NH); ^{13}C NMR (50 MHz, DMSO-d_6) δ 56.0 (CH_3), 39.5 (CH_2), 48.1 (CH_2), 105.6 (CH), 121.7 (CH), 123.6 (CH), 126.5 (C), 128.0 (CH), 128.7 (CH), 130.0 (CH), 130.9 (CH), 132.6 (C), 132.7 (C), 133.6 (CH), 134.6 (C), 142.2 (C), 143.6 (C), 161.5 (C). Anal. Calcd for $C_{18}H_{18}N_4O$: C, 70.57; H, 5.92; N, 18.29. Found: C, 70.32; H, 5.62; N, 18.52.

***N*-(2,3-Dichloroisoindolo[2,1-*a*]quinoxalin-6-yl)ethane-1,2-diamine (9c)**. Brown solid; yield: 60%; mp 164 °C; IR ($CHBr_3$) ν 3671, 3584 (NH_2), 3419 (NH) cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 3.76-3.80 (m, 2H, CH_2), 4.92 (t, *J* 6.4 Hz, 2H, CH_2), 7.78-7.97 (m, 3H, Ar-H), 8.20 (s, 1H, Ar-H), 8.32 (s, 1H, Ar-H), 8.54 (dd, *J* 1.2, 7.4 Hz, 1H, Ar-H), 8.92 (d, *J* 1.2 Hz, 1H, Ar-H), 11.25 (br, 1H, NH); ^{13}C NMR (50 MHz, $CDCl_3$) δ 40.0 (CH_2), 48.7 (CH_2), 119.1 (C), 124.8 (CH), 127.5 (C), 128.6 (CH), 128.8 (CH), 129.5 (CH), 129.6 (CH), 131.9 (CH), 132.4 (C), 132.9 (C), 133.7 (CH), 135.5 (C), 138.1 (C), 139.7 (C), 161.9 (C). Anal. Calcd for $C_{17}H_{14}Cl_2N_4$: C, 59.14; H, 4.09; N, 16.23. Found: C, 58.86; H, 4.15; N, 16.47.

***N*-(2-Methylisoindolo[2,1-*a*]quinoxalin-6-yl)ethane-1,2-diamine (9d).** Yellow solid; yield: 64%; mp 168 °C; IR ($CHBr_3$) ν 3689, 3567 (NH_2), 3372 (NH) cm^{-1}; ^1H NMR (200 MHz, DMSO-d_6) δ 2.73 (s, 3H, CH_3), 3.78-3.83 (m, 2H, CH_2), 4.78 (t, *J* 6.4 Hz, 2H, CH_2), 7.62-8.05 (m, 6H, Ar-H), 8.40 (dd, *J* 0.9, 7.8 Hz, 1H, Ar-H), 8.85 (dd, *J* 0.9, 7.8 Hz, 1H, Ar-H), 11.24 (br,

1H, NH); ^{13}C NMR (50 MHz, DMSO-d_6) δ 16.7 (CH_3), 39.6 (CH_2), 47.8 (CH_2), 124.0 (CH), 126.6 (CH), 127.1 (C), 127.5 (CH), 128.2 (CH), 129.8 (CH), 130.8 (CH), 131.5 (CH), 132.3 (C), 133.6 (CH), 135.5 (C), 138.5 (C), 139.1 (C), 142.2 (C), 161.1 (C). Anal. Calcd for $C_{18}H_{18}N_4$: C, 74.46; H, 6.25; N, 19.30. Found: C, 74.72; H, 6.01; N, 19.07.

2-(6-Iminoisoindolo[2,1-*a*]quinoxalin-5(6*H*)-yl)ethanamine (9a). White solid; yield: 72%; mp 194 °C; IR ($CHBr_3$) ν 3679, 3556 (NH_2), 3393 (NH), 1719 (C=NH) cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 3.83 (t, *J* 4.9 Hz, 2H, CH_2), 5.05 (t, *J* 4.9 Hz, 2H, CH_2), 7.80-7.92 (m, 4H, Ar-H), 8.01 (td, *J* 1.4, 7.3 Hz, 1H, Ar-H), 8.27-8.35 (m, 2H, Ar-H), 8.43 (dd, *J* 0.8, 7.9 Hz, 1H, Ar-H), 9.25 (dd, *J* 0.8, 7.9 Hz, 1H, Ar-H), 11.32 (br, 1H, NH); ^{13}C NMR (50 MHz, $CDCl_3$) δ 50.2 (CH_2), 66.5 (CH_2), 124.6 (CH), 125.2 (CH), 125.3 (CH), 129.1 (C), 129.2 (C), 129.2 (CH), 129.3 (CH), 129.4 (CH), 129.5 (C), 129.7 (C), 130.4 (CH), 130.9 (CH), 132.2 (C), 132.8 (CH), 136.8 (C). Anal. Calcd for $C_{17}H_{16}N_4$: C, 73.89; H, 5.84; N, 20.27. Found: C, 73.96; H, 6.01; N, 19.93.

2-(6-Imino-3-methoxyisoindolo[2,1-*a*]quinoxalin-5(6*H*)-yl)ethanamine (9b). White solid; yield: 62%; mp 198.8 °C; IR ($CHBr_3$) ν 3584, 3437 (NH_2), 3319 (NH), 1666 (C=NH) cm^{-1}; ^{1}H NMR (200 MHz, DMSO-d_6) δ 3.77 (t, *J* 6.2 Hz, 2H, CH_2), 3.98 (s, 3H, OCH_3), 4.77 (t, *J* 6.2 Hz, 2H, CH_2), 7.35-7.46 (m, 2H, Ar-H), 7.70-8.09 (m, 4H, 4 x Ar-H), 8.37 (d, *J* 7.5 Hz, 1H, Ar-H), 8.80 (d, *J* 7.5 Hz, 1H, Ar-H), 11.30 (br, 1H, NH); ^{13}C NMR (50 MHz, DMSO-d_6) δ 39.5 (CH_2), 48.1 (CH_2), 56.0 (CH_3), 105.6 (CH), 121.6 (CH), 123.6 (CH), 126.4 (C), 128.0 (CH), 129.9 (CH), 130.9 (CH), 131.7 (CH), 132.5 (C), 132.6 (C), 133.6 (CH), 134.5 (C), 142.2 (C), 143.6 (C), 161.2 (C). Anal. Calcd for $C_{18}H_{18}N_4O$: C, 70.57; H, 5.92; N, 18.29. Found: C, 70.83; H, 5.68; N, 18.01.

2-(2,3-Dichloro-6-iminoisoindolo[2,1-*a*]quinoxalin-5(6*H*)-yl)ethanamine (9c). Brown solid; yield: 78%; mp 182 °C; IR ($CHBr_3$) ν 3679, 3558 (NH_2), 3393 (NH), 1719 (C=NH) cm^{-1}; ^{1}H NMR (200 MHz, DMSO-d_6) δ 3.92 (t, *J* 5.0 Hz, 2H, CH_2), 4.90 (t, *J* 5.0 Hz, 2H, CH_2), 7.94-8.14 (m, 3H, Ar-H), 8.35 (d, *J* 8.1 Hz, 1H, Ar-H), 8.47 (s, 1H, Ar-H), 8.57 (s, 1H, Ar-H), 9.05 (d, *J* 8.1 Hz, 1H, Ar-H), 11.31 (br, 1H, NH); ^{13}C NMR (50 MHz, DMSO-d_6) δ 50.1 (CH_2), 66.8 (CH_2), 122.9 (C), 124.9 (CH), 125.6 (CH), 129.4 (CH), 129.7 (CH), 131.4 (CH), 132.9 (CH), 133.9 (C), 134.5 (C), 135.2 (C), 139.8 (C), 141.8 (C), 143.1 (CH), 163.6 (C), 164.5 (C). Anal. Calcd for $C_{17}H_{14}Cl_2N_4$: C, 59.14; H, 4.09; N, 16.23. Found: C, 59.41; H, 4.36; N, 16.02.

2-(6-Imino-2-methylisoindolo[2,1-*a*]quinoxalin-5(6*H*)-yl)ethanamine (9d). Yellow solid; yield: 64%; mp 189.6 °C; IR ($CHBr_3$) ν 3604, 3501 (NH_2), 3407 (NH), 1713 (C=NH) cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 2.98 (s, 3H, CH_3), 3.82 (t, *J* 4.9 Hz, 2H, CH_2), 5.08 (t, *J* 4.9 Hz, 2H, CH_2), 7.60-7.80 (m, 3H, Ar-H), 7.87 (td, *J* 2.4, 7.4 Hz, 1H, Ar-H), 8.00 (td, *J* 1.4, 7.9 Hz, 1H, Ar-H), 8.17 (dd, *J* 2.4, 7.4 Hz, 1H, Ar-H), 8.43 (dd, *J* 1.3, 8.1 Hz, 1H, Ar-H), 9.25 (d, *J* 7.8 Hz, 1H, Ar-H), 11.39 (br, 1H, NH); ^{13}C NMR (50 MHz, $CDCl_3$) δ 18.0 (CH_3), 29.7 (CH_2), 50.3 (CH_2), 122.6 (CH), 124.7 (CH), 125.3 (CH), 127.2 (CH), 129.1 (CH), 130.2 (CH), 130.6 (CH), 132.4 (CH), 135.0 (C), 137.1 (C), 137.4 (C), 141.4 (C), 142.6 (C), 146.7 (C), 162.8 (C). Anal. Calcd for $C_{18}H_{18}N_4$: C, 74.46; H, 6.25; N, 19.30. Found: C, 74.82; H, 6.17; N, 19.01.

General procedure for the preparation of substituted 1-(5-bromopyridin-2-yl)-3-[2-(isoindolo[2,1-*a*]quinoxalin-6-ylamino)ethyl]thioureas (3a-d) and 1-(5-bromopyridin-2-yl)-

3-[2-(6-iminoisoindolo[2,1-a]quinoxalin-5(6*H*)-yl)ethyl]thioureas (4a-d). To a suspension of 5-bromo-2-isothiocyanatopyridine[41] (4.0 mmol) in DMF (15 mL) the suitable *N*-(isoindolo[2,1-*a*]quinoxalin-6-yl)ethane-1,2-diamine **9a-d** or 2-(6-iminoisoindolo[2,1-*a*]quinoxalin-5(6*H*)-yl)ethanamine **10a-d** (1.0 mmol) was added and the reaction was stirred at 100 °C for 16 hours. Then the reaction mixture was cooled to room temperature, poured into iced water and the resulting precipitate collected by filtration. The crude obtained was purified by column chromatography to give derivatives **3a-d** and **4a-d**.

1-(5-Bromopyridin-2-yl)-3-[2-(isoindolo[2,1-*a*]quinoxalin-6-ylamino)ethyl]thiourea (3a). The residue eluted with DCM/Ethyl acetate 9/1. White solid; yield: 65%; mp 198 °C; IR ($CHBr_3$) ν 3678 (NH), 3563 (NH), 3403 (NH), 1328 (C=S) cm^{-1}; ^1H NMR (200 MHz, DMSO-d_6) δ 4.19-4.22 (m, 2H, CH_2), 4.89-4.91 (m, 2H, CH_2), 6.76 (d, *J* 9.1 Hz, 1H, Ar-H), 7.67-7.69 (m, 2H, Ar-H), 7.71-7.87 (m, 3H, Ar-H), 7.84-7.92 (m, 2H, Ar-H), 7.99-8.03 (m, 1H, Ar-H), 8.06-8.13 (m, 1H, Ar-H), 8.35 (d, *J* 7.5 Hz, 1H, Ar-H), 8.89 (d, *J* 7.5 Hz, 1H, Ar-H), 10.42 (br, 1H, NH), 10.62 (br, 1H, NH), 11.21 (t, *J* 4.9 Hz, 1H, NH); ^{13}C NMR (50 MHz, DMSO-d_6) δ 40.3 (CH_2), 42.8 (CH_2), 111.5 (C), 113.8 (CH), 113.9 (CH), 124.0 (CH), 127.4 (CH), 127.9 (CH), 128.2 (CH), 128.5 (CH), 130.7 (CH), 131.4 (CH), 132.4 (C), 133.4 (CH), 135.4 (C), 138.2 (C), 140.0 (C), 140.7 (CH), 144.0 (C), 145.2 (CH), 151.7 (C), 161.4 (C), 180.0 (C). Anal. Calcd for $C_{23}H_{19}BrN_6S$: C, 56.22; H, 3.90; N, 17.10. Found: C, 56.39; H, 3.76; N, 17.43.

1-(5-Bromopyridin-2-yl)-3-{2-[(3-methoxyisoindolo[2,1-*a*]quinoxalin-6-yl)amino]ethyl} thiourea (3b). The residue eluted with DCM/Ethyl acetate 9/1. White solid; yield: 63%; mp 239 °C; IR ($CHBr_3$) ν 3688 (NH), 3584 (NH), 3405 (NH), 1360 (C=S) cm^{-1}; ^1H NMR (200 MHz, DMSO-d_6) δ 4.37 (s, 3H, OCH_3), 4.62-4.64 (m, 2H, CH_2), 5.30-5.36 (m, 2H, CH_2), 7.20 (d, *J* 8.6 Hz, 1H, Ar-H), 7.58 (d, *J* 2.7 Hz, 1H, Ar-H), 7.78 (dd, *J* 2.7, 8.6 Hz, 1H, Ar-H), 8.09-8.31 (m, 4H, Ar-H), 8.38-8.46 (m, 2H, Ar-H), 8.77 (d, *J* 7.9 Hz, 1H, Ar-H), 9.25 (d, *J* 7.9 Hz, 1H, Ar-H), 10.72 (br, 1H, NH), 10.86 (br, 1H, NH), 11.64 (t, *J* 4.7 Hz, 1H, NH); ^{13}C NMR (50 MHz, DMSO-d_6) δ 40.7 (CH_2), 43.9 (CH_2), 56.7 (CH_3), 106.2 (CH), 112.4 (CH), 114.8 (CH), 122.3 (CH), 124.5 (CH), 127.7 (C), 128.8 (CH), 130.6 (CH), 131.6 (CH), 133.4 (C), 133.7 (C), 134.3 (CH), 135.1 (C), 141.6 (CH), 142.9 (C), 145.1 (C), 146.1 (CH), 152.6 (C), 162.1 (C), 162.4 (C), 180.9 (C). Anal. Calcd for $C_{24}H_{21}BrN_6OS$: C, 55.28; H, 4.06; N, 16.12. Found: C, 55.52; H, 3.86; N, 16.42.

1-(5-Bromopyridin-2-yl)-3-{2-[(2,3-dichloroisoindolo[2,1-*a*]quinoxalin-6-yl)amino]ethyl} thiourea (3c). The residue eluted with DCM. Pale yellow solid; yield: 85%; mp 235 °C; IR ($CHBr_3$) ν 3671 (NH), 3558 (NH), 3414 (NH), 1311 (C=S) cm^{-1}; ^1H NMR (200 MHz, DMSO-d_6) δ 4.19-4.23 (m, 2H, CH_2), 4.86-4.88 (m, 2H, CH_2), 6.77 (d, *J* 8.8 Hz, 1H, Ar-H), 7.68-7.75 (m, 2H, Ar-H), 7.84 (s, 1H, Ar-H), 7.89-8.08 (m, 3H, Ar-H), 8.35-8.39 (m, 2H, Ar-H), 8.83 (d, *J* 7.7 Hz, 1H, Ar-H), 10.01 (br, 1H, NH), 10.43 (br, 1H, NH), 11.18 (t, *J* 4.9 Hz, 1H, NH); ^{13}C NMR (50 MHz, DMSO-d_6) δ 40.1 (CH_2), 42.9 (CH_2), 111.7 (CH), 113.8 (CH), 121.9 (C), 124.2 (CH), 127.7 (CH), 127.9 (CH), 128.0 (C), 129.1 (CH), 129.4 (C), 130.5 (C), 131.9 (C), 132.1 (CH), 133.2 (C), 133.6 (CH), 137.0 (C), 138.8 (C), 140.7 (CH), 145.1 (C), 145.2 (CH), 147.7

(C), 181.7 (C). Anal. Calcd for $C_{23}H_{17}BrCl_2N_6S$: C, 49.30; H, 3.06; N, 15.00. Found: C, 49.02; H, 3.33; N, 14.72.

1-(5-Bromopyridin-2-yl)-3-{2-[(2-methylisoindolo[2,1-*a*]quinoxalin-6-yl)amino]ethyl} thiourea (3d). The residue eluted with DCM/Ethyl acetate 98/2. Pale yellow solid; yield: 75%; mp 230 °C; IR ($CHBr_3$) ν 3757 (NH), 3570 (NH), 3406 (NH), 1297 (C=S) cm^{-1}; ^1H NMR (200 MHz, DMSO-d_6) δ 2.71 (s, 3H, CH_3), 4.23-4.25 (m, 2H, CH_2), 4.90-4.95 (m, 2H, CH_2), 6.77 (d, *J* 8.9 Hz, 1H, Ar-H), 7.44 (d, *J* 2.4 Hz, 1H, Ar-H), 7.60-7.67 (m, 3H, Ar-H), 7.85-8.13 (m, 4H, Ar-H), 8.38 (d, *J* 7.8 Hz, 1H, Ar-H), 8.89 (d, *J* 7.9 Hz, 1H, Ar-H), 10.47 (br, 1H, NH), 10.62 (br, 1H, NH), 11.12 (t, *J* 5.8 Hz, 1H, NH); ^{13}C NMR (50 MHz, DMSO-d_6) δ 16.7 (CH_3), 42.7 (CH_2), 59.7 (CH_2), 111.5 (CH), 113.8 (CH), 123.9 (CH), 126.2 (CH), 127.4 (CH), 127.9 (CH), 131.3 (CH), 132.4 (CH), 133.4 (CH), 134.9 (C), 135.5 (C), 138.2 (C), 139.0 (C), 140.7 (CH), 141.4 (C), 142.9 (C), 144.9 (CH), 151.6 (C), 161.4 (C), 170.3 (C), 179.9 (C). Anal. Calcd for $C_{24}H_{21}BrN_6S$: C, 57.03; H, 4.19; N, 16.63. Found: C, 56.82; H, 4.49; N, 16.32.

1-(5-Bromopyridin-2-yl)-3-[2-(6-iminoisoindolo[2,1-*a*]quinoxalin-5(6*H*)-yl)ethyl]thiourea (4a). The residue eluted with DCM/Ethyl acetate 9/1. Pale yellow solid; yield: 68%; mp 205 °C; IR ($CHBr_3$) ν 3670 (NH), 3557 (NH), 1704 (C=NH), 1323 (C=S) cm^{-1}; ^1H NMR (200 MHz, DMSO-d_6) δ 3.74-3.80 (m, 2H, CH_2), 4.80 (t, *J* 6.1 Hz, 2H, CH_2), 7.38 (d, *J* 8.0 Hz, 1H, Ar-H), 7.83-7.95 (m, 3H, Ar-H), 8.01-8.10 (m, 2H, Ar-H), 8.16-8.25 (m, 3H, Ar-H), 8.42 (d, *J* 8.0 Hz, 1H, Ar-H), 8.61 (d, *J* 2.5 Hz, 1H, Ar-H), 8.90 (d, *J* 8.0 Hz, 1H, Ar-H) 10.25 (br, 1H, NH), 11.30 (br, 1H, NH), 11.38 (t, *J* 5.3 Hz, 1H, NH); ^{13}C NMR (50 MHz, DMSO-d_6) δ 39.7 (CH_2), 48.1 (CH_2), 118.9 (C), 121.7 (CH), 124.1 (CH), 127.1 (C), 127.5 (C), 127.6 (CH), 127.9 (CH), 128.1 (CH), 128.6 (CH), 128.8 (CH), 131.2 (CH), 131.7 (CH), 132.4 (C), 133.7 (CH), 135.6 (C), 138.5 (C), 140.2 (C), 142.1 (CH), 143.5 (C), 150.7 (CH), 161.2 (C). Anal. Calcd for $C_{23}H_{19}BrN_6S$: C, 56.22; H, 3.90; N, 17.10. Found: C, 56.38; H, 4.07; N, 16.88.

1-(5-Bromopyridin-2-yl)-3-[2-(6-imino-3-methoxyisoindolo[2,1-*a*]quinoxalin-5(6*H*)-yl)ethyl] thiourea (4b). The residue eluted with DCM/Ethyl acetate 9/1. White solid; yield: 67%; mp 243 °C; IR ($CHBr_3$) ν 3680 (NH), 3558 (NH), 1696 (C=NH), 1297 (C=S) cm^{-1}; ^1H NMR (200 MHz, DMSO-d_6) δ 3.95 (s, 3H, OCH_3), 4.16-4.24 (m, 2H, CH_2), 4.90 (t, *J* 5.1 Hz, 2H, CH_2), 6.77 (d, *J* 8.6 Hz, 1H, Ar-H), 7.15 (d, *J* 2.7 Hz, 1H, Ar-H), 7.35 (dd, *J* 2.7, 8.6 Hz, 1H, Ar-H), 7.67-7.74 (m, 2H, Ar-H), 7.84 (t, *J* 7.4 Hz, 1H, Ar-H), 7.95-8.10 (m, 3H, Ar-H), 8.35 (d, *J* 7.4 Hz, 1H, Ar-H), 8.83 (d, *J* 7.4 Hz, 1H, Ar-H), 10.44 (br, 1H, NH), 11.22 (t, *J* 5.4 Hz, 1H, NH), 11.28 (br, 1H, NH); ^{13}C NMR (50 MHz, DMSO-d_6) δ 39.7 (CH_2), 43.0 (CH_2), 55.8 (CH_3), 105.2 (CH), 111.5 (C), 113.8 (CH), 121.3 (CH), 123.5 (CH), 126.8 (C), 127.8 (CH), 127.9 (CH), 129.6 (CH), 130.7 (CH), 132.5 (C), 132.7 (C), 133.3 (CH), 134.2 (C), 140.7 (CH), 141.9 (C), 144.1 (C), 145.2 (CH), 151.7 (C), 161.1 (C), 161.4 (C). Anal. Calcd for $C_{24}H_{21}BrN_6OS$: C, 55.28; H, 4.06; N, 16.12. Found: C, 55.53; H, 3.85; N, 16.42.

1-(5-Bromopyridin-2-yl)-3-[2-(2,3-dichloro-6-iminoisoindolo[2,1-*a*]quinoxalin-5(6*H*)-yl)ethyl] thiourea (4c). The residue eluted with DCM. Pale yellow solid; yield: 78%; mp 228 °C; IR ($CHBr_3$) ν 3576 (NH), 3394 (NH), 1669 (C=NH), 1297 (C=S) cm^{-1}; ^1H NMR (200 MHz, DMSO-d_6) δ 4.15-4.20 (m, 2H, CH_2), 4.87 (t, *J* 5.6 Hz, 2H, CH_2), 6.77 (d, *J* 8.4 Hz, 1H, Ar-H),

7.67-7.75 (m, 2H, 2 x Ar-H), 7.84 (s, 1H, Ar-H), 7.85-8.08 (m, 3H, Ar-H), 8.35-8.39 (m, 2H, Ar-H), 8.83 (d, *J* 7.0 Hz, 1H, Ar-H), 10.27 (br, 1H, NH), 10.43 (br, 1H, NH), 11.18 (t, *J* 5.6 Hz, 1H, NH); ^{13}C NMR (50 MHz, DMSO-d_6) δ 40.1 (CH_2), 42.9 (CH_2), 111.7 (C), 113.8 (CH), 116.4 (CH), 117.1 (C), 118.3 (C), 124.2 (CH), 127.7 (CH), 127.8 (CH), 128.0 (C), 129.1 (CH), 130.6 (C), 132.0 (CH), 133.2 (C), 133.6 (CH), 136.9 (C), 138.8 (C), 140.7 (CH), 145.1 (CH), 147.6 (C), 151.1 (C), 161.5 (C). Anal. Calcd for $C_{23}H_{17}BrCl_2N_6S$: C, 49.30; H, 3.06; N, 15.00. Found: C, 49.17; H, 3.34; N, 15.32.

1-(5-Bromopyridin-2-yl)-3-[2-(6-imino-2-methylisoindolo[2,1-*a*]quinoxalin-5(6*H*)-yl)ethyl] thiourea (4d). The residue eluted with DCM. Pale yellow solid; yield: 81%; mp 241 °C; IR ($CHBr_3$) ν 3570 (NH), 3384 (NH), 1674 (C=NH), 1343 (C=S) cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 2.78-2.80 (m, 5H, CH_2CH_3), 3.43-3.47 (m, 2H, CH_2), 7.61-7.64 (m, 2H, Ar-H), 7.77-8.05 (m, 6H, Ar-H), 8.42-8.54 (m, 3H, Ar-H), 9.01 (t, *J* 5.0 Hz, 1H, NH), 9.22 (br, 1H, NH), 9.27 (br, 1H, NH); ^{13}C NMR (50 MHz, $CDCl_3$) δ 17.3 (CH_3), 24.8 (CH_2), 29.7 (CH_2), 77.2 (CH), 108.3 (C), 115.4 (C), 120.1 (CH), 124.8 (CH), 127.3 (CH), 128.0 (CH), 128.3 (CH), 130.9 (CH), 131.2 (CH), 133.6 (CH), 133.9 (C), 134.7 (CH), 135.9 (C), 140.5 (C), 140.9 (CH), 141.9 (C), 149.4 (C), 154.8 (C), 162.1 (C), 165.1 (C). Anal. Calcd for $C_{24}H_{21}BrN_6S$: C, 57.03; H, 4.19; N, 16.63. Found: C, 56.83; H, 4.43; N, 16.91.

References

1. De Clercq, E. *Curr. Med. Chem.* **2001**, *13*, 1543-1572. http://dx.doi.org/10.2174/0929867013371842
2. Tarby, C. M. *Curr. Top. Med. Chem*. **2004**, *4*, 1045-1057. http://dx.doi.org/10.2174/1568026043388295
3. Moyle, G. *Drugs* **2001**, *61*, 19-26. http://dx.doi.org/10.2165/00003495-200161010-00003
4. Huang, H.; Chopra, R.; Verdine, G. L.; Harrison, S. C. *Science* **1998**, *282*, 1669-1677. http://dx.doi.org/10.1126/science.282.5394.1669
5. Esnouf, R.; Ren, J.; Ross, C.; Jones, Y.; Stammers, D.; Stuart, D. *Nat. Struct. Biol*. **1995**, *2*, 303-308. http://dx.doi.org/10.1038/nsb0495-303
6. Das, K.; Lewi, P. J.; Hughes, S. H.; Arnold, E. *Prog. Biophys. Mol. Biol*. **2005**, *88*, 209-231. http://dx.doi.org/10.1016/j.pbiomolbio.2004.07.001
7. Sarafianos, S. G.; Das, K.; Hughes, S. H.; Arnold, E. *Curr. Opin. Struct. Biol*. **2004**, *14*, 716-730. http://dx.doi.org/10.1016/j.sbi.2004.10.013
8. Menendez-Arias, L. *Antiviral Res*. **2010**, *85*, 210-231. http://dx.doi.org/10.1016/j.antiviral.2009.07.006
9. Zhan, P.; Liu, X.; Li, Z. *Curr. Med. Chem.* **2009**, *16*, 2876-2889. http://dx.doi.org/10.2174/092986709788803231

10. Song, Y.; Fang, Z.; Liu, X. *Curr. Med. Chem.* **2014**, *21*, 329-355. http://dx.doi.org/10.2174/09298673113206660298
11. Patidar, A. K.; Jeyakandan M.; Mobiya A. K.; Selvam, G. *Int. J. Pharmtech Research* **2011**, *3*, 386-392.
12. Kleim, J. P.; Bender, R.; Billhardt, U. M.; Meichsner, C.; Riess, G.; Rosner, M.; Winkler, I.; Paessens, A. *Antimicrob. Agents Chemother*. **1993**, *37*, 1659-1664. http://dx.doi.org/10.1128/AAC.37.8.1659
13. Kleim, J. P.; Winters, M.; Dunkler, A.; Suarez, J-R.; Riess, G.; Winkler, I.; Balzarini, J.; Oette, D.; Merigan, T. C and the HBY 097/2001 Study Group. *J. Infec. Dis*. **1999**, *179*, 709-713. http://dx.doi.org/10.1086/314633
14. Ren, J.; Nichols, C. E.; Chamberlain, P. P.; Weaver, K. L.; Short, S. A.; Chan, J. H.; Kleim, J-P.; Stammers, D. K. *J. Med. Chem*. **2007**, *50*, 2301-2309. http://dx.doi.org/10.1021/jm061117m
15. Xu, B.; Sun, Y.; Guo, Y.; Cao, Y.; Yu, T. *Bioorg. Med. Chem*. **2009**, *17*, 2767-2774. http://dx.doi.org/10.1016/j.bmc.2009.02.039
16. Campiani, G.; Aiello, F.; Fabbrini, M.; Morelli, E.; Ramunno, A.; Armaroli, S.; Nacci, V.; Garofalo, A.; Greco, G.; Novellino, E.; Maga, G.; Spadari, S.; Bergamini, A.; Ventura, L.; Bongiovanni, B.; Capozzi, M.; Bolacchi, F.; Marini, S.; Coletta, M.; Guiso, G.; Caccia, S. *J. Med. Chem*. **2001**, *44*, 305-315. http://dx.doi.org/10.1021/jm0010365
17. Barraja, P.; Diana, P.; Lauria, A.; Montalbano, A.; Almerico, A. M.; Dattolo, G.; Cirrincione, G.; Viola, G.; Dall'Acqua, F. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 2809-2811. http://dx.doi.org/10.1016/S0960-894X(03)00529-8
18. Barraja, P.; Caracausi, L.; Diana, P.; Carbone, A.; Montalbano, A.; Cirrincione, G.; Brun, P.; Palù, G.; Castagliuolo, I.; Dall'Acqua, F.; Vedaldi, D.; Salvador A. *Bioorg. Med. Chem.* **2010**, *18*, 4830-4843. http://dx.doi.org/10.1016/j.bmc.2010.04.080
19. Barraja, P.; Caracausi, L.; Diana, P.; Montalbano, A.; Carbone, A.; Salvador, A.; Brun, P.; Castagliuolo, I.; Tisi, S.; Dall'Acqua, F.; Vedaldi, D.; Cirrincione, G. *Chem. Med. Chem.* **2011**, *6*, 1238-1248. http://dx.doi.org/10.1002/cmdc.201100085
20. Barraja, P.; Diana, P.; Spanò, V.; Montalbano, A.; Carbone, A.; Parrino, B.; Cirrincione G. *Tetrahedron* **2012**, *68*, 5087-5094. http://dx.doi.org/10.1016/j.tet.2012.04.041
21. Carbone, A.; Parrino, B.; Barraja, P.; Spanò, V.; Cirrincione, G.; Diana, P.; Maier, A.; Kelter, G.; Fiebig H-H. *Marine Drugs* **2013**, *11*, 643-654. http://dx.doi.org/10.3390/md11030643
22. Barraja, P.; Spanò, V.; Diana, P.; Carbone, A.; Cirrincione, G. *Tetrahedron Lett.* **2009**, *50*, 5389-5391. http://dx.doi.org/10.1016/j.tetlet.2009.07.045

23. Barraja, P.; Diana, P.; Montalbano, A.; Carbone, A.; Viola, G.; Basso, G.; Salvador, A.; Vedaldi, D.; Dall'Acqua, F.; Cirrincione, G. *Bioorg. Med. Chem.* **2011**, *19*, 2326-2341. http://dx.doi.org/10.1016/j.bmc.2011.02.023
24. Spanò, V.; Montalbano, A.; Carbone, A.; Parrino, B.; Diana, P.; Cirrincione, G.; Castagliuolo, I.; Brun, P.; Issinger, O-G.; Tisi, S.; Primac, I.; Vedaldi, D.; Salvador, A.; Barraja, P. *Eur. J. Med. Chem*. **2014**, *74*, 340-357. http://dx.doi.org/10.1016/j.ejmech.2013.10.014
25. Barraja, P.; Diana, P.; Carbone, A.; Cirrincione G. *Tetrahedron* **2008**, *64*, 11625-11631. http://dx.doi.org/10.1016/j.tet.2008.10.022
26. Lauria, A.; Patella, C.; Diana, P.; Barraja, P.; Montalbano, A.; Cirrincione, G.; Dattolo, G.; Almerico, A. M. *Heterocycles* **2003**, *60*, 2669-2675. http://dx.doi.org/10.3987/COM-03-9877
27. Diana, P.; Stagno, A.; Barraja, P.; Carbone, A.; Parrino, B.; Dall'Acqua, F.; Vedaldi, D.; Salvador, A.; Brun, P.; Castagliuolo, I.; Issinger, O. G.; Cirrincione, G *Chem. Med. Chem.* **2011**, *6*, 1291-1299. http://dx.doi.org/10.1002/cmdc.201100027
28. Barraja, P.; Caracausi, L.; Diana, P.; Spanò, V., Montalbano, A.; Carbone, A.; Parrino, B.; Cirrincione, G. *Chem. Med. Chem.* **2012**, *7*, 1901-1904. http://dx.doi.org/10.1002/cmdc.201200296
29. Diana, P.; Carbone, A.; Barraja, P.; Montalbano, A.; Martorana, A.; Dattolo, G.; Gia, O.; Dalla Via, L.; Cirrincione, G. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 2342-2346. http://dx.doi.org/10.1016/j.bmcl.2007.01.065
30. Diana, P.; Carbone, A.; Barraja, P.; Martorana, A.; Gia, O.; Dalla Via, L.; Cirrincione, G. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 6134-6137. http://dx.doi.org/10.1016/j.bmcl.2007.09.042
31. Diana, P., Carbone, A.; Barraja, P.; Kelter, G.; Fiebig, H.-H.; Cirrincione, G. *Bioorg. Med. Chem.* **2010**, *18*, 4524-4529. http://dx.doi.org/10.1016/j.bmc.2010.04.061
32. Diana, P.; Carbone, A.; Barraja, P.; Montalbano, A.; Parrino, B.; Lopergolo, A.; Pennati, M.; Zaffaroni, N; Cirrincione, G. *Chem. Med. Chem.* **2011**, *6*, 1300-1309. http://dx.doi.org/10.1002/cmdc.201100078
33. Carbone, A.; Pennati, M.; Parrino, B.; Lopergolo, A.; Barraja, P.; Montalbano, A.; Spanò, V.; Sbarra, S.; Doldi, V.; De Cesare, M.; Cirrincione, G.; Diana, P.; Zaffaroni, N. *J. Med. Chem.* **2013**, *56*, 7060-7072. http://dx.doi.org/10.1021/jm400842x
34. Carbone, A.; Pennati, M.; Barraja, P.; Montalbano, A.; Parrino, B.; Spanò, V.; Lopergolo, A.; Sbarra, S.; Doldi, V.; Zaffaroni, N.; Cirrincione, G.; Diana, P. *Curr. Med. Chem.* **2014**, *21*, 1654-1666. http://dx.doi.org/10.2174/09298673113206660307
35. Barraja, P.; Spanò, V.; Diana, P.; Carbone, A.; Cirrincione, G.; Vedaldi, D.; Salvador A.; Viola, G.; Dall'Acqua F. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 1711-1714. http://dx.doi.org/10.1016/j.bmcl.2009.01.096

36. Diana, P.; Martorana, A.; Barraja, P.; Lauria, A.; Montalbano, A.; Almerico, A. M.; Dattolo, G.; Cirrincione, G. *Bioorg. Med. Chem.* **2007**, *15*, 343-349. http://dx.doi.org/10.1016/j.bmc.2006.09.054
37. Diana, P.; Martorana, A.; Barraja, P.; Montalbano, A.; Dattolo, G.; Cirrincione, G.; Dall'Acqua, F.; Salvador, A.; Vedaldo, D.; Basso, G.; Viola, G. *J. Med. Chem.* **2008**, *51*, 2387-2399. http://dx.doi.org/10.1021/jm070834t
38. Cirrincione, G.; Diana, P.; Parrino, B.; Carbone, A. Italian Patent RM2013A000588.
39. Barraja, P.; Spanò, V.; Giallombardo, D.; Diana, P.; Montalbano, A.; Carbone, A.**;** Parrino, B. Cirrincione, G. *Tetrahedron* **2013**, *69*, 6474-6477. http://dx.doi.org/10.1016/j.tet.2013.05.083
40. MacLeod, F.; Lang, S.; Murphy, J. A. *Synlett* **2010**, 529-534.
41. Song, Y.; Zhu, B.; Bhakta, C.; Scarborough, R.M. PTC Int. Appl. 063293, 2006; *Chem. Abstr*. **2003**, *139*, 240348.

