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Note

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Multicomponent one pot synthesis of 3-tetrazolyl and 3-imidazo[1,2-*a*]pyridin tetrazolo[1,5-*a*]quinolines

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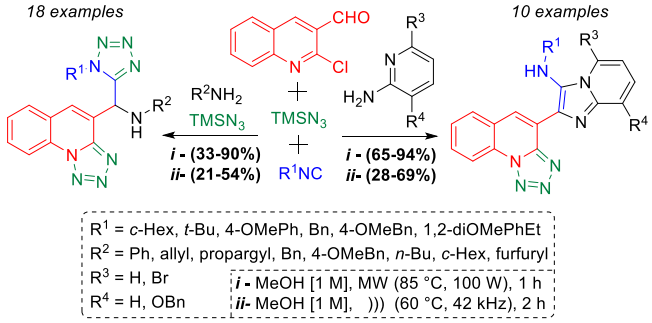


ABSTRACT

A series of eighteen 3-tetrazolyl-tetrazolo[1,5-*a*]quinolines were synthesized in 21 to 90% yields via a novel one pot Ugi-azide / S_NAr / ring-chain azido-tautomerization process. We report also the synthesis of ten 3-imidazo[1,2-*a*]pyridin-tetrazolo[1,5-*a*]quinolines in 28 to 94% yields via a novel one pot Groebke-Blackburn-Bienaymé / S_NAr / ring-chain azido-tautomerization process. Both synthetic strategies involve the use of microwaves or ultrasound, and catalyst-free conditions. Finally, we show the synthesis of the tetrazolo[1,5-*a*]quinoline-3-carbaldehyde and tetrazolo[1,5-*a*]quinoline-3-dimethyl acetal at room temperature in methanol as solvent.

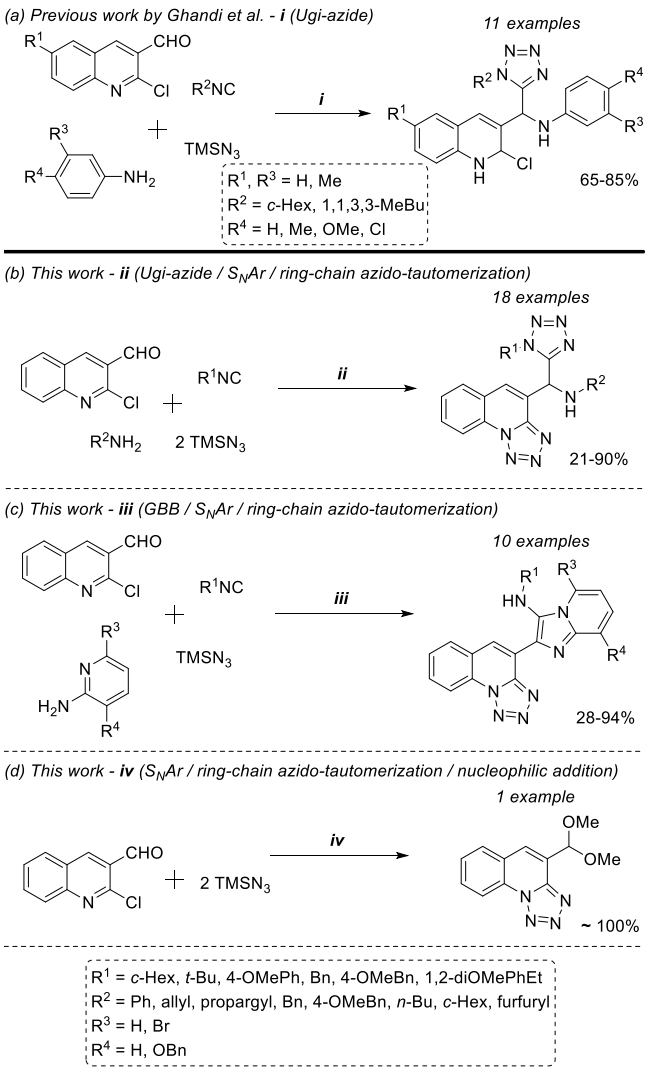
Bis-heterocycles are compounds containing two fused, merged, linked, or bound heterocyclic moieties.[1] These molecules have attracted much attention of scientific community from various fields such as agrochemistry, materials science, optics, medicinal chemistry, and others emerging areas.[2,3] In this note, we report the one pot synthesis of novel unsymmetrical *bis*–heterocycles containing the tetrazolo[1,5-*a*]quinoline core bound with either, 1,5-disubstituted-tetrazole (1,5-DS-T) or imidazo[1,2-*a*]pyridine frameworks.

Tetrazolo[1,5-*a*]quinoline is the core of various compounds with interesting pharmacological properties, for example, anti-cancer,[4] anti-fungal,[5] anti-bacterial,[6] and anti-inflammatory.[6] Particularly, there is a tetrazolo[1,5-*a*]quinoline bound with a tetrazole ring, which exhibited anti-allergic activity.[7] Moreover, 1,5-DS-T's are considered metabolic resistant bioisosters of the *cis*-amide bond of peptides by adopting their effective biological conformations.[8-9] Thus, 1,5-DS-T is the core of numerous bioactive products.[10] As examples, Cefamandole and Latamoxeb, which are second- and third-generation cephalosporin antibiotics, respectively.[11] Besides, imidazo[1,2-*a*]pyridine framework is present also in a plethora of drugs, but mainly in various treatments of brain diseases and CNS-related disorders.[12] For example, the zolpidem, which is the most prescribed drug for insomnia.[13]

The general method to synthesize tetrazolo[1,5-*a*]quinolines involves a two-step process S_NAr / ring-chain azido-tautomerization using as starting reagents sodium azide and 2-chloroquinolines prepared stepwise.[14] Besides, 1,5-DS-T are synthesized using click reactions between organic azides and nitriles, both usually synthesized stepwise.[15] In the same context, there are various reported methods to synthesize imidazo[1,2-*a*]pyridines, generally form precursors prepared stepwise.[16] However, the Ugi-azide and the interrupted variant of the Ugi-4CR known as Groebke-Blackburn-Bienaymé (GBB) reaction are the current and most efficient methods to synthesize 1,5-DS-T[17] and imidazo[1,2-*a*]pyridines,[18] respectively.

As far as we know, the synthesis of unsymmetrical *bis*-heterocycles containing the tetrazolo[1,5-*a*]quinoline framework bound either, with 1,5-DS-T or imidazo[1,2-*a*]pyridine moieties have not been reported using MCR or any other stepwise method. However, there is a previous work by Ghandi *et al.* describing the synthesis of 3-tetrazolyl-2-chloroquinolines in 65 to 85% yields via Ugi-azide reaction (Scheme 1a).[19]

Thus, according to our ongoing program to develop Ugi-azide based methods toward *bis*-heterocycles containing 1,5-DS-T rings,[20-24] we report the first synthesis of 3-tetrazolyl-tetrazolo[1,5-*a*]quinolines and 3-imidazo[1,2-*a*]pyridin-tetrazolo[1,5-*a*]quinolines via one pot Ugi-type / S_NAr / ring-chain azido-tautomerization processes (Scheme 1b-c). In the same context, we developed a new one pot method to synthesize the tetrazolo[1,5-*a*]quinoline-3-carbaldehyde either, as aldehyde or protected as dimethyl acetal (Scheme 1d). This latter masked aldehyde can be used for further transformations, in which the tetrazolo[1,5-*a*]quinoline system is required.

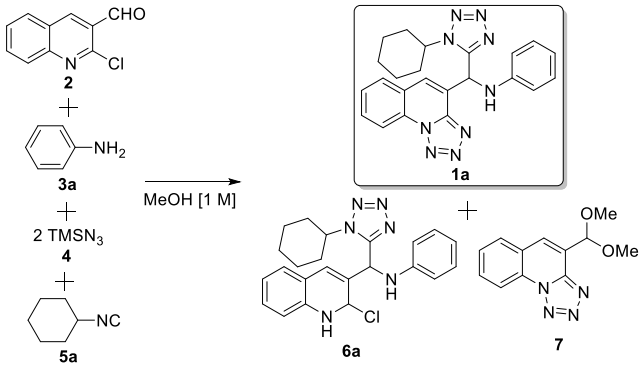


Scheme 1. Synthetic strategies

The *N*-((1-cyclohexyl-1*H*-tetrazol-5-yl)(tetrazolo[1,5-*a*]quinolin-4-yl)methyl)prop-2-en-1-amine (**1a**) was selected as model to optimize reaction conditions (Table 1). Thus, 2-chloroquinoline-3-carbaldehyde (**2**) was combined sequentially with one equivalent of aniline (**3a**), two equivalents of azidotrimethyilsilane (**4**), and one equivalent of cyclohexyl isocyanide (**5a**) using the Ugi-azide standard conditions (MeOH, rt) as starting point. The product **1a** was isolated in 18% yield, together with products **6a** and **7** in 40 and 16% yields respectively (Entry 1, Table 1). Then, we decided to study the effect of temperature because it has been reported that ring-chain azido-tautomerization is favored to cyclic tautomer (tetrazole) by using high temperatures.[25] Thus, the reaction was performed in methanol at reflux, but the product **1a** was synthesized in 55% yield, together with **6a** and **7** in 10 and 4% yields respectively (Entry 2, Table 1). In this context, we used microwaves (MW) as heat source in order to reduce the reaction time and

eventually to increase the yields. The product **1a** was synthesized in 75% yield without by-products (Entry 3, Table 1). Only traces of the corresponding Schiff base (formed by condensation of 2-chloroquinoline-3-carbaldehyde (**2**) with aniline (**3a**)) were observed. A further experiment was performed increasing temperature to 110 °C by MW, but the yield was 68% without by-products (Entry 4, Table 1). Finally, an experiment was performed using ultrasound (US) irradiation (or sonication), but the yield was 44% without by-products (Entry 5, Table 1). It is important to mention that a change in the order of addition was done ($TMSN_3$ (**4**) after isocyanide **5a**) using the optimal conditions of Entry 3, but the yield remained without changes. This latter observation gave us elements to propose a plausible reaction mechanism (*See the supporting information for further details*).

Table 1. Screening conditions



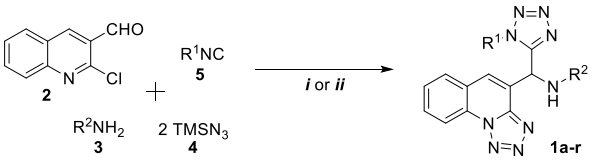
Entry	*T* (°C)	*t* (h)	Yield[c] (%)		
			1a	**6a**	**7**
1	rt	24	18	40	16
2	85	12	55	10	4
3	85[a]	1	75	-	-
4	110[a]	1	68	-	-
5	60[b]	2	44	-	-

[a] MW (100 W). [b] US (42 kHz). [c] Measured after purification.

By using optimal conditions for the two irradiation methods (MW and US), we synthesized the 3-tetrazolyl-tetrazolo[1,5-*a*]quinolines **1a-r** (Table 2). As seen, good substrate scope was found. The stereoelectronic nature of substituents in starting materials varies from alkyl to aryl and benzyl substituents in isocyanide moiety. Besides, amines with a variety in their stereoelectronic nature (aromatic, aliphatic, allylic, propargylic, benzylic and heterocyclic) were also explored to synthesize a set of eighteen final products. With respect to MW heating method, higher yields were observed for 3,4-dimethoxyphenethyl isocyanide derivatives (**1f**, 88 and **1l**, 90%) while the lowest was for the cyclohexyl isocyanide derivative (**1r**, 65 %), which contains furfuryl as substituent coming from the amine moiety. As seen, similar results were found using US irradiation because higher yields were observed for 3,4-

dimethoxyphenethyl isocyanide derivatives (**1f**, 51 and **1l**, 54%), while the lowest was also for the cyclohexyl isocyanide derivative (**1r**, 21 %) containing furfuryl ring. Overall, the yields obtained in MW assisted reactions were higher (33-90%) with respect to those observed using sonication (21-54%). Besides, it is noteworthy that compounds **6a-r** can be synthesized using only one equivalent of $TMSN_3$ instead two, but the tetrazolo[1,5-*a*]quinoline-3-dimethyl acetal **7** will be formed as by-product. Adequate crystals for X-ray analysis of compounds **1b** (CCDC: 1431691) and **6b** (CCDC: 1482686) were obtained.

Table 2. Substrate scope



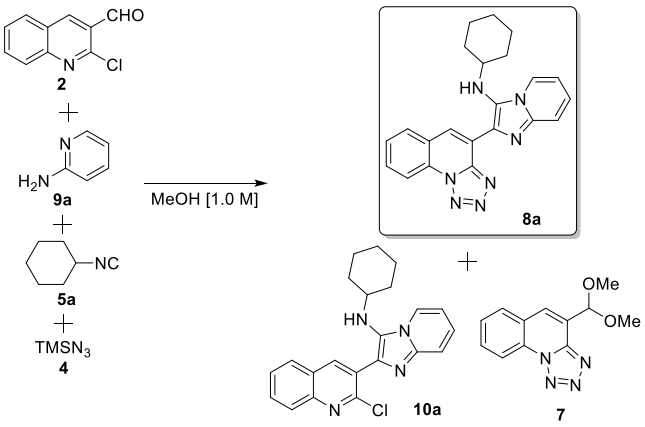
Compound	R^1	R^2	Yield[i] (%)	Yield[ii] (%)
1a	*c*-Hex	Ph	75	41
1b	*t*-Bu	Ph	88	38
1c	4-OMePh	Ph	62	27
1d	Bn	Ph	84	47
1e	4-OMeBn	Ph	65	29
1f	3,4-diMePhEt	Ph	88	51
1g	*c*-Hex	Allyl	87	44
1h	*t*-Bu	Allyl	78	30
1i	4-OMePh	Allyl	65	29
1j	Bn	Allyl	74	34
1k	4-OMeBn	Allyl	81	39
1l	3,4-diMePhEt	Allyl	90	54
1m	*c*-Hex	Propargyl	74	35
1n	*c*-Hex	Bn	61	32
1o	*c*-Hex	4-OMeBn	57	30
1p	*c*-Hex	*n*-Bu	51	33
1q	*c*-Hex	*c*-Hex	41	26
1r	*c*-Hex	furfuryl	33	21

[i] MeOH [1 M], MW (85 °C, 100 W), 1 h.
[ii] MeOH [1 M], US (60 °C, 42 kHz), 2 h.

Continuing with our study, we selected the *N*-cyclohexyl-2-(tetrazolo[1,5-*a*]quinolin-4-yl)imidazo[1,2-*a*]pyridin-3-amine (**8a**) as model to optimize the one pot process GBB / S_NAr / ring-chain azido-tautomerization. Thus, 2-chloroquinoline-3-carbaldehyde (**2**) was combined sequentially with one equivalent of all, 2-aminopyridine (**9a**), cyclohexyl isocyanide (**5a**), and azidotrimethylsilane (**4**) in methanol [1 M] at room temperature (Entry 1, Table 3). The *bis*-heterocycle **8a** was isolated in 25% yield, together with product **10a** and the tetrazolo[1,5-*a*]quinoline-3-dimethyl acetal (**7**), in 30 and 18% yields respectively. It is noteworthy that adequate crystals for x-ray analysis of

compound **8a** (CCDC: 1470205) were obtained. Then, according to our previous observations, we decided to conduct the process at reflux, but the compound **8a** was synthesized in 82% yield after 12 hours without by-products (Entry 2, Table 3). The reaction was performed using microwaves as heat source, yielding 94% after 1 hour. A further experiment was conducted increasing temperature to 110 °C, but the product **8a** was isolated in 76% yield (Entry 4, Table 3). Finally, an experiment was performed under US irradiation, but the yield was 47% without by-products (Entry 5, Table 1). Besides, an experiment to synthesize exclusively the compound **10a** was conducted using conditions of entry 3, but without addition of trimethylsylilazide (**4**). Compound **10a** was isolated in quantitative yield. The plausible reaction mechanism can be found in the *Supporting Information File*.

Table 3. Screening conditions



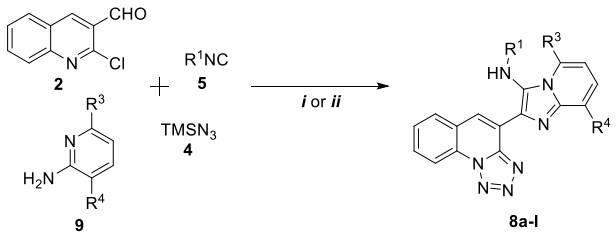
Entry	Solvent	*T* (°C)	*t* (h)	Yield[c] (%)		
				8a	**10a**	**7a**
1	MeOH	rt	24	25	30	18
2	MeOH	85	12	82	-	-
3	MeOH	85[a]	1	94	-	-
4	MeOH	110[a]	1	76	-	-
5	MeOH	60[b]	2	47	-	-

[a] MW (100 W). [b] US (42 kHz).
[c] Measured after purification.

By using optimized conditions for the two irradiation methods (MW and US), we synthesized the series of 3-imidazo[1,2-*a*]pyridin-tetrazolo[1,5-*a*]quinolines **8a-l** (Table 4). As seen, good to excellent yields were obtained (67-94%) under MW heating conditions, and moderate to good yields (28-69%) under sonication. It is noteworthy that products **8f** and **8k** could not be synthesized. We calculated minimal energy conformations for both compounds by Density Functional Theory at M06–2X/6–311G(d) level of theory (*See the supporting information for further details*). Compound **8f** was not synthesized due to the steric hindrance between the bulky *tert*-butyl moiety and bromine atom

coming from the 6-bromo-2-aminopyridine moiety. There is a previous study by us regarding this type of behavior for the GBB reaction involving similar substituents.[26] Respect to the non-synthesized product **8k**, there is also a strong steric strain between tetrazolo[1,5-*a*]quinoline moiety and the N-H coming from the isocyanide moiety.

Table 4. Substrate scope

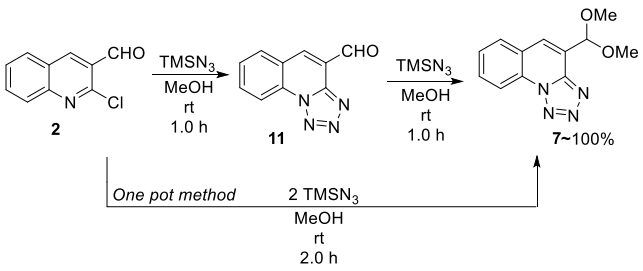


Compound	R^1	R^3	R^4	Yield[i] (%)	Yield[ii] (%)
8a	*c*-Hex	H	H	94	47
8b	*t*-Bu	H	H	86	55
8c	4-OMePh	H	H	79	44
8d	Bn	H	H	91	54
8e	*c*-Hex	Br	H	89	69
8f	*t*-Bu	Br	H	0	0
8g	4-OMePh	Br	H	67	31
8h	Bn	Br	H	77	34
8i	*c*-Hex	H	OBn	75	59
8j	*t*-Bu	H	OBn	65	28
8k	4-OMePh	H	OBn	0	0
8l	Bn	H	OBn	69	32

[i] MeOH [1 M], MW (85 °C, 100 W), 1 h.
[ii] MeOH [1 M], US (60 °C, 42 kHz), 2 h.

To conclude the work, we show the synthesis of the tetrazolo[1,5-*a*]quinoline-3-dimethyl acetal (**7**) in quantitative yield. 2-chloroquinoline-3-carbaldehyde (**2**) was used as starting reagent and methanol as solvent via S_NAr / ring-chain azido-tautomerization process with azidotrimethylsilane (**4**) to give the tetrazolo[1,5-*a*]quinoline-3-carbaldehyde (**11**), which undergoes a hydrazoic acid-catalyzed protection of the aldehyde functional group via nucleophilic addition (Scheme 2). As seen, tetrazolo[1,5-*a*]quinoline-3-cabaldehyde (**11**) can be prepared using 1 equiv. of $TMSN_3$ in 1 hour and the tetrazolo[1,5-*a*]quinoline-3-dimethyl acetal (**7**) adding 1 equiv. more of $TMSN_3$ to **11** in one hour more, or in one pot manner from 2-chloroquinoline-3-carbaldehyde (**2**) using 2 equiv. of $TMSN_3$ in 2 hours. Protection of aldehyde moiety depends on the amount of HN_3 (formed by proton exchange between MeOH and $TMSN_3$ (**4**)). Conditions to synthesize **7** are greener in comparison to current reported methodologies, which are stepwise and involve the use of harsh conditions like high temperatures and metallic Lewis catalysts in longer reaction

time.[27] Adequate crystals for X-ray analysis of the tetrazolo[1,5-*a*]quinoline-3-dimethyl acetal (**7**) (CCDC: 1482685) were obtained.



Scheme 2. Synthesis of tetrazolo[1,5-a]quinoline-3-dimethyl acetal and its non-protected analog

As conclusions, methodologies herein described are sustainable processes with potential application in the synthesis of *bis*-heterocycles containing the tetrazolo[1,5-*a*]quinoline framework from complex precursors prepared *in situ* in one pot manner. The most important feature of this work lies in the development of novel strategies in which MCR reactions as Ugi-azide and GBB were combined with cascade S_NAr / ring-chain azido-tautomerization processes taking place in mild and green conditions toward *bis*-heterocycles type tetrazolo[1,5-*a*]quinolines containing both, 1,5-DS-T and imidazo[1,2-*a*]pyridine moieties. The synthesis of *bis*-heterocycles involved the combination of three processes: Ugi-type / S_NAr / ring-chain azido tautomerization to introduce high complex substituents at C-5 position of tetrazoles, C-3 of imidazo[1,2-*a*]pyridines and in C-3 of tetrazolo[1,5-*a*]quinolines. Reactions performed under microwave heating conditions gave higher yields than those using sonication.

EXPERIMENTAL SECTION

General Information. ^1H and ^{13}C NMR spectra were acquired on 400 or 500 MHz spectrometers. The solvent for NMR samples was $CDCl_3$. Chemical shifts are reported in parts per million (δ/ppm). Internal reference for NMR spectra is TMS at 0.00 ppm. Coupling constants are reported in Hertz (*J*/Hz). Multiplicities of the signals are reported using the standard abbreviations: singlet (s), doublet (d), triplet (t), quartet (q) and multiplet (m). IR spectra were recorded by ATR method using neat compounds. The wavelengths are reported in reciprocal centimeters (ν_{max} /cm^{-1}). HRMS spectra were acquired via electrospray ionization ESI (+) and recorded via the TOF method. Reactions at reflux were performed using a recirculation system mounted on a sand bath with electronic temperature control. Microwave assisted reactions were performed in closed vessel mode using a CEM Discover™ monomodal MW reactor without pressure sensor. Ultrasound irradiated reactions were performed using a recirculation system mounted

into bath of a Branson 1510 sonicator cleaner working at 42 kHz ±6% frequencies. The reaction progress was monitored by TLC and the spots were visualized under UV light (254 or 365 nm). Flash column chromatography was performed using silica gel (230-400 mesh) and mixtures in different proportions of hexanes with ethyl acetate as mobile phase. Melting points were determined on a Fisher-Johns apparatus and were uncorrected. Purity degree is documented product-by-product qualitatively with copies of all NMR spectra. Commercially available reagents were used without further purification. Solvents were distilled and dried according to standard procedures.

Procedure (*i*) to synthesize the products 1a-r (MW): In a vial (10 mL) equipped with a magnetic stirring bar containing a solution of 2-chloroquinoline-3-carbaldehyde (0.52 mmol, 1.0 equiv.) in anhydrous MeOH [1.0 M], were added sequentially the corresponding amine (0.52 mmol, 1.0 equiv.), azidotrimethylsilane (1.56 mmol, 3.0 equiv.) and the corresponding isocyanide (0.52 mmol, 1.0 equiv.). Then, the vial was closed and the reaction mixture was MW-heated at 85 ^{o}C (100 W) for 1 hour. The solvent was removed until dryness and the crude was purified by silica-gel column chromatography using mixtures of hexanes with ethyl acetate (7/3; *v/v*) to afford products **1a-r**.

Procedure (*ii*) to synthesize the products 1a-r (US): In a round-bottomed flask (10 mL) equipped with condenser containing a solution of 2-chloroquinoline-3-carbaldehyde (0.52 mmol, 1.0 equiv.) in anhydrous MeOH [1.0 M], were added sequentially the corresponding amine (0.52 mmol, 1.0 equiv.), azidotrimethylsilane (1.56 mmol, 3.0 equiv.) and the corresponding isocyanide (0.52 mmol, 1.0 equiv.). Then, the flask was closed and the reaction mixture was sonicated at 60 ^{o}C (45 kHz) for 2 hours. Then, the solvent was removed until dryness and the crude was purified by silica-gel column chromatography using mixtures of hexanes with ethyl acetate (7/3; *v/v*) to afford products **1a-r**.

Procedure (*i*) to synthesize the products 8a-l (MW): In a vial (10 mL) equipped with a magnetic stirring bar containing a solution of 2-chloroquinoline-3-carbaldehyde (0.51 mmol, 1.0 equiv.) in anhydrous MeOH [1 M], were added sequentially the corresponding amine (0.52 mmol, 1.0 equiv.), the corresponding isocyanide (0.52 mmol, 1.0 equiv.), and azidotrimethylsilane (1.56 mmol, 3.0 equiv.). Then, the vial was closed and the reaction mixture was MW-heated at 85 ^{o}C (100 W) for 1 hour. Then, the solvent was removed until dryness and the crude was purified by silica-gel column chromatography using mixtures of hexanes with ethyl acetate (7/3; *v/v*) to afford products **8a-l**.

Procedure (*ii*) to synthesize the products 8a-l (US): In a round-bottomed flask (10 mL) equipped with condenser containing a solution of 2-chloroquinoline-3-carbaldehyde (0.51 mmol, 1.0 equiv.) in anhydrous MeOH [1 M], were added sequentially the corresponding amine (0.52 mmol, 1.0 equiv.), the corresponding isocyanide (0.52 mmol, 1.0 equiv.), and azidotrimethylsilane (1.56 mmol, 3.0 equiv.). Then, the flask was closed and the reaction mixture was sonicated at 60 ^{o}C (45 kHz) for 2 hours. Then, the solvent was removed until dryness and the crude was purified by silica-gel column chromatography using mixtures of hexanes with ethyl acetate (7/3; *v/v*) to afford products **8a-l**.

Procedure to synthesize the product 7: In a round-bottomed flask (10 mL) equipped with a magnetic stirring bar containing a solution of 2-chloroquinoline-3-carbaldehyde (0.52 mmol, 1.0 equiv.) in anhydrous MeOH [1.0 M] under argon atmosphere at room temperature, were added 2 equiv. of azidotrimethylsilane (0.52 mmol, 1.0 equiv.). The flask was closed and the reaction mixture was stirred at room temperature for 2 hours. Then, the solvent was removed until dryness and the crude was recrystallized using a cold mixture of hexanes with diethyl ether (1/1; *v/v*) to afford the product **7**.

***N*-((1-cyclohexyl-1*H*-tetrazol-5-yl)(tetrazolo[1,5-*a*]quinolin-4-yl)methyl)aniline** (**1a**): Pale brown solid (83.0 mg, 75%, MW) (45.4 mg, 41%, US); mp = 174–175 °C; R_f = 0.40 (Hexanes-AcOEt = 7/3 *v/v*); ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.69 (d, *J* = 8.4 Hz, 1H), 8.14 (s, 1H), 7.92 (d, *J* = 8.0 Hz, 1H), 7.89–7.83 (m, 1H), 7.72–7.65 (m, 1H), 7.54–7.46 (m, 1H), 7.17–7.07 (m, 2H), 6.75–6.68 (m, 1H), 6.56 (d, *J* = 7.8 Hz, 1H), 5.71–5.67 (m, 1H), 5.62–5.57 (m, 1H), 3.75–3.64 (m, 1H), 1.97–1.92 (m, 1H), 1.75–1.70 (m, 1H), 1.62–1.56 (m, 2H), 1.55–1.47 (m, 2H), 1.39–1.28 (m, 2H), 1.22–1.15 (m, 1H), 1.05–0.99 (m, 1H); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$): δ 153.4, 146.4, 144.7, 131.5, 131.3, 130.2, 129.7, 129.4, 128.3, 128.1, 123.9, 123.8, 123.6, 123.3, 119.8, 116.8, 116.7, 114.0, 58.7, 54.4, 33.5, 32.8, 25.2 (2), 24.8; FT-IR (ATR)ν_{max}/cm^{-1} 3287.4 (N-H), 1602.0 (C=N), 1256.1 (N-N=N); HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{23}H_{24}N_9$ 426.2149; Found 426.2153.

***N*-((1-(tert-butyl)-1*H*-tetrazol-5-yl)(tetrazolo[1,5-*a*]quinolin-4-yl)methyl)aniline** (**1b**): White solid (183.0 mg, 88%, MW) (79.0 mg, 38%, US); mp = 166–168 °C; R_f = 0.36 (Hexanes-AcOEt = 7/3 *v/v*); ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.65 (d, *J* = 8.4 Hz, 1H), 8.24 (s, 1H), 7.95 (d, *J* = 8.0 Hz, 1H), 7.89–7.83 (m, 1H), 7.71–7.65 (m, 1H), 7.21–7.14 (m, 2H), 6.92 (d, *J* = 8.7 Hz, 1H), 6.83–6.78 (m, 1H), 6.76 (d, *J* = 7.9 Hz, 2H), 4.93 (d, *J* = 8.9 Hz, 1H), 1.92 (s, 9H), 1.64 (bs, 1H); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$): δ 153.4, 146.7, 144.6, 131.3, 131.1, 130.4, 129.8, 129.7, 129.6, 128.7, 128.2, 123.9, 123.6, 119.9, 116.7, 113.8, 62.8, 49.2, 30.2; FT-IR (ATR)ν_{max}/cm^{-1} 3287 (N–H), 1602 (C=N), 1256 (N–N=N); HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{21}H_{22}N_9$ 400.1992; Found 400.1991.

Precursor of compound **1b**: *N*-((2-chloro-1,2-dihydroquinolin-3-yl)(1-cyclohexyl-1*H*-tetrazol-5-yl)methyl)aniline (**6b**): white solid (125.2 mg, ~100%, MW), mp = 201–202 °C; R_f = 0.30 (Hexanes-AcOEt = 7/3 *v/v*); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.32 (s, 1H), 8.03 (d, *J* = 8.2 Hz, 1H), 7.80–7.71 (m, 2H), 7.58–7.49 (m, 1H), 7.21–7.13 (m, 2H), 6.83–6.77 (m, 1H), 6.73–6.66 (m, 2H), 6.56 (d, *J* = 8.9 Hz, 1H), 4.84 (d, *J* = 8.7 Hz, 1H), 1.79 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$, TMS): δ 153.6, 149.1, 147.4, 144.7, 137.9, 131.1, 129.7, 129.6, 128.2, 128.1, 127.5, 127.2, 119.8, 113.9, 62.7, 51.1, 30.0; FT-IR (ATR)ν_{max}/cm^{-1} 3285 (N–H), 1598 (C=N), 1260 (N–N=N); HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{21}H_{22}ClN_6$ 393.1588; Found 393.1580.

***N*-((1-(4-methoxyphenyl)-1*H*-tetrazol-5-yl)(tetrazolo[1,5-*a*]quinolin-4-yl)methyl)aniline** (**1c**): Brown solid (72.0 mg, 62%, MW) (31.4 mg, 27%, US); mp = 68–70 °C; R_f = 0.33 (Hexanes-AcOEt = 7/3 *v/v*); ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.90 (s, 1H), 8.66 (d, *J* = 8.3 Hz, 1H), 8.23 (s, 1H), 7.97 (d, *J* = 8.0 Hz, 1H), 7.90–7.85 (m, 1H), 7.74–7.68 (m, 1H), 7.62–7.56 (m, 5H), 7.15–7.11 (m, 2H), 7.07 (d, *J* = 9.0 Hz, 4H), 7.03 (d, *J* = 9.0 Hz, 2H), 6.82–6.78 (m, 1H), 6.65 (d, *J* = 7.8 Hz, 2H), 6.54 (d, *J* = 9.0 Hz, 1H), 4.90 (d, *J* = 9.3 Hz, 1H), 3.89 (s, 3H); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$): δ 161.3, 154.7, 144.7, 140.6, 131.4, 130.9, 129.8, 129.6, 129.5, 129.0, 128.9, 128.8, 128.2, 127.1, 125.8, 123.8, 122.9, 119.9, 116.6, 115.2, 115.0, 114.2, 55.7, 48.2; FT-IR (ATR) ν_{max}/cm^{-1} 3287 (N–H), 1602.8 (C=N), 1256.6 (N-N=N); HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{24}H_{20}N_9O$ 450.1785; Found 450.1787.

***N*-((1-benzyl-1*H*-tetrazol-5-yl)(tetrazolo[1,5-*a*]quinolin-4-yl)methyl)aniline** (**1d**): Orange solid (95.0 mg, 84%, MW) (53.2 mg, 47%, US); mp = 75–76 °C; R_f = 0.43 (Hexanes-AcOEt = 4/1 *v/v*); ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.62 (d, *J* = 8.3 Hz, 1H), 8.05 (s, 1H), 7.92–7.82 (m, 2H), 7.70–7.65 (m, 1H), 7.16 (s, 5H), 7.12–7.08 (m, 2H), 6.80–6.73 (m, 1H), 6.56 (d, *J* = 8.2 Hz, 2H), 6.45 (d, *J* = 7.9 Hz, 1H), 6.05 (d, *J* = 15.4 Hz, 1H), 5.89 (d, *J* = 15.4 Hz, 1H), 5.17 (d, *J* = 7.9 Hz, 1H); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$): δ 154.4, 146.6, 144.7, 133.1, 131.8, 131.4, 130.5, 129.7, 129.6, 129.1, 128.9, 128.5, 127.7, 123.9, 123.1, 120.0, 116.9, 114.1, 52.0, 48.9; FT-IR (ATR) ν_{max}/cm^{-1} 3287.1 (N-H), 1613.4 (C=N), 1288.5 (N-N=N); HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{24}H_{20}N_9$ 434.1836; found 434.1841.

***N*-((1-(4-methoxybenzyl)-1*H*-tetrazol-5-yl)(tetrazolo[1,5-*a*]quinolin-4-yl)methyl)aniline** (**1e**): Orange solid (79.0 mg, 65%, MW) (35.2 mg, 29%, US); mp = 77–78 °C; R_f = 0.40 (Hexanes-AcOEt = 7/3 *v/v*); ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.91 (s, 1H), 8.64 (d, *J* = 8.4 Hz, 1H), 8.24 (s, 1H), 7.96 (d, *J* = 7.8 Hz, 1H), 7.90–7.84 (m, 1H), 7.73–7.67 (m, 1H), 7.62–7.55 (m, 5H), 7.16–7.10 (m, 2H), 7.07 (d, *J* = 9.0 Hz, 4H), 7.03 (d, *J* = 9.0 Hz, 2H), 6.83–6.77 (m, 1H), 6.65 (d, *J* = 7.8 Hz, 2H), 6.53 (d, *J* = 8.7 Hz, 1H), 5.03 (d, *J* = 9.2 Hz, 1H), 3.89 (s, 3H); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$): δ 154.2, 146.4, 144.6, 133.0, 131.6, 131.3, 130.3, 129.5, 129.4, 129.0, 128.8, 128.3, 127.6, 123.7, 123.0, 119.9, 116.7, 114.0, 113.6, 51.9, 48.8, 29.3; FT-IR (ATR) ν_{max}/cm^{-1} 3287 (N–H), 1613 (C=N), 1288 (N–N=N); HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{25}H_{22}N_9O$ 464.1941; Found 464.1934.

***N*-((1-(3,4-dimethoxyphenethyl)-1*H*-tetrazol-5-yl)(tetrazolo[1,5-*a*]quinolin-4-yl)methyl)aniline** (**1f**): Brown solid (183.0 mg, 88%, MW) (106.1 mg, 51%, US); mp = 113–115 °C; R_f = 0.44 (Hexanes-AcOEt = 7/3 *v/v*); ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.62 (d, *J* = 8.4 Hz, 1H), 7.98 (s, 1H), 7.89 (d, *J* = 8.02 Hz, 1H), 7.87–7.82 (m, 1H), 7.69–7.64 (m, 1H), 7.15–7.05 (m, 2H), 6.78–6.69 (m, 1H), 6.59–6.48 (m, 5H), 6.39–6.37 (m, 1H), 5.90 (d, *J* = 7.9 Hz, 1H), 5.30 (s, 1H), 5.12 (d, *J* = 7.9 Hz, 1H), 5.10–5.04 (m, 1H), 4.96–4.87 (m, 1H), 3.72 (s, 3H), 3.63 (s, 3H); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$): δ 154.7, 149.2, 148.2, 146.4, 144.4, 131.5, 131.4, 130.3, 129.5, 129.4, 128.7, 128.3, 123.8, 123.0,

120.7, 119.7, 116.7, 113.8, 111.7, 111.4, 55.8, 55.7, 49.9, 48.3, 36.0; FT-IR (ATR) ν_{max}/cm^{-1} 3287.2 (N–H), 1602.8 (C=N), 1256.6 (N–N=N); HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{27}H_{26}N_9O_2$ 508.2203; Found 508.2208.

***N*-((1-cyclohexyl-1*H*-tetrazol-5-yl)(tetrazolo[1,5-*a*]quinolin-4-yl)methyl)prop-2-en-1-amine** (**1g**): White solid (176.0 mg, 87%, MW) (89.0 mg, 44%, US); mp = 177–178 °C; R_f = 0.48 (Hexanes-AcOEt = 7/3 *v/v*); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.66 (d, *J* = 8.29 Hz, 1H), 8.18 (s, 1H), 7.99 (d, *J* = 7.98 Hz, 1H), 7.91–7.85 (m, 1H), 7.75–7.68 (m, 1H), 5.96–5.82 (m, 2H), 5.23–5.15 (m, 2H), 4.83–4.72 (m, 1H), 3.36–3.28 (m, 2H), 2.74 (bs, 1H), 2.18–2.05 (m, 2H), 2.03–1.88 (m, 4H), 1.57–1.42 (m, 2H), 1.39–1.27 (m, 1H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 153.9, 146.9, 135.3, 131.6, 131.4, 130.4, 129.5, 128.5, 124.1, 123.9, 117.9, 116.9, 58.6, 51.2, 50.2, 33.5, 33.0, 25.5, 25.4, 24.9; FT-IR (ATR) ν_{max}/cm^{-1} 3309 (N–H), 1615 (N=C), 1288 (N–N=N); HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{20}H_{24}N_9$ 390.2149; Found 390.2154.

***N*-((1-(*tert*-butyl)-1*H*-tetrazol-5-yl)(tetrazolo[1,5-*a*]quinolin-4-yl)methyl)prop-2-en-1-amine** (**1h**): White solid (148.0 mg, 78%, MW) (56.9 mg, 30%, US); mp = 119–121 °C; R_f = 0.36 (Hexanes-AcOEt = 7/3; *v/v*); ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.68 (d, *J* = 8.3 Hz, 2H), 8.09 (d, *J* = 7.7 Hz, 1H), 7.95–7.90 (m, 1H), 7.76–7.71 (m, 1H), 6.56 (s, 1H), 6.18–6.02 (m, 1H), 5.47–5.33 (m, 2H), 3.81 (bs, 1H), 3.46–3.37 (m, 1H), 1.78 (s, 9H); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$): δ 154.2, 147.1, 135.3, 131.4, 131.4, 130.3, 129.4, 128.3, 124.7, 123.8, 117.7, 116.8, 62.2, 52.0, 50.5, 30.1; FT-IR (ATR) ν_{max}/cm^{-1} 3335 (N–H), 1642 (N=H), 1273 (N–N=N); HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{18}H_{22}N_9$ 364.1992; Found 364.1997.

***N*-((1-(4-methoxyphenyl)-1*H*-tetrazol-5-yl)(tetrazolo[1,5-*a*]quinolin-4-yl)methyl)prop-2-en-1-amine** (**1i**): Yellow solid (167.0 mg, 65%, MW) (74.5 mg, 29%, US); mp = 141–143 °C; R_f = 0.37 (Hexanes-AcOEt = 7/3 *v/v*); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.66 (d, *J* = 8.3 Hz, 1H), 8.24 (s, 1H), 8.00 (d, *J* = 7.9 Hz, 1H), 7.91–7.86 (m, 1H), 7.76–7.70 (m, 1H), 7.62 (d, *J* = 8.6 Hz, 2H), 7.04 (d, *J* = 8.6 Hz, 2H), 5.84 (s, 1H), 5.79–5.67 (m, 1H), 5.05–4.92 (m, 2H), 3.88 (s, 3H), 3.29–3.18 (m, 2H), 2.46 (s, 1H); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 161.5, 155.5, 146.9, 135.1, 131.6, 131.3, 130.5, 129.6, 128.4, 127.3, 126.3, 124.1, 123.9, 117.7, 116.9, 115.2, 55.9, 50.6, 50.1; FT-IR (ATR) ν_{max}/cm^{-1} 3289 (N–H), 1614 (C=N), 1304 (N–N=N); HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{21}H_{20}N_9O$ 414.1785; Found 414.1789.

***N*-((1-benzyl-1*H*-tetrazol-5-yl)(tetrazolo[1,5-*a*]quinolin-4-yl)methyl)prop-2-en-1-amine** (**1j**): Yellow solid (154.0 mg, 74%, MW) (70.8 mg, 34%, US); mp = 128–130 °C; R_f = 0.42 (Hexanes-AcOEt = 4/1 *v/v*); ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.61 (d, *J* = 8.1 Hz, 1H), 7.91–7.82 (m, 3H), 7.70–7.65 (m, 1H), 7.21–7.12 (m, 5H), 6.01 (d, *J* = 15.3 Hz, 1H), 5.83 (d, *J* = 15.3 Hz, 1H), 5.79–5.71 (m, 2H), 5.10–5.02 (m, 2H), 3.15–3.01 (m, 2H), 2.67 (s, 1H); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$): δ 154.8, 146.7, 134.9, 133.5, 131.5, 131.3, 129.3, 128.9, 128.6, 128.2, 127.7, 123.7, 123.6,

121.6, 117.5, 116.7, 51.6, 50.1, 41.9; FT-IR (ATR) ν_{max}/cm^{-1} 3064 (N–H), 1617 (C=N), 1274 (N–N=N); HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{21}H_{20}N_9$ 398.1836; Found 398.1844.

***N*-((1-(4-methoxybenzyl)-1*H*-tetrazol-5-yl)(tetrazolo[1,5-*a*]quinolin-4-yl)methyl)prop-2-en-1-amine** (**1k**): Pale yellow solid (90.0 mg, 81%, MW) (43.3 mg, 39%, US); mp = 137–138 °C; R_f = 0.42 (Hexanes-AcOEt = 7/3 *v/v*); ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.59 (d, *J* = 8.2 Hz, 1H), 7.85–7.81 (m, 2H), 7.76 (s, 1H), 7.69–7.64 (m, 1H), 7.07 (d, *J* = 8.6 Hz, 2H), 6.57 (d, *J* = 8.6 Hz, 2H), 5.90 (d, *J* = 15.1 Hz, 1H), 5.83–5.74 (m, 2H), 5.67 (d, *J* = 8.6 Hz, 1H), 5.11–5.09 (m, 1H), 5.08–5.05 (m, 1H), 3.63 (s, 3H), 3.12 (dq, *J* = 13.9, 6.0 Hz, 2H); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$): δ 159.8, 154.6, 146.8, 135.1, 131.5, 131.4, 130.2, 129.4, 129.3, 128.4, 125.3, 123.8, 123.6, 117.7, 116.7, 114.1, 55.3, 51.7, 51.3, 50.3; FT-IR (ATR) ν_{max}/cm^{-1} 3311 (N–H), 1613 (C=N), 1305 (N–N=N); HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{22}H_{22}N_9O$ 428.1941; Found 428.1947.

***N*-((1-(3,4-dimethoxyphenethyl)-1*H*-tetrazol-5-yl)(tetrazolo[1,5-*a*]quinolin-4-yl)methyl)prop-2-en-1-amine** (**1l**): Yellow solid (110.0 mg, 90%, MW) (66.0 mg, 54%, US); mp = 118–119 °C; R_f = 0.40 (Hexanes-AcOEt = 7/3 *v/v*); ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.66 (d, *J* = 8.4 Hz, 1H), 7.94 (d, *J* = 7.9 Hz, 1H), 7.92–7.86 (m, 2H), 7.75–7.70 (m, 1H), 6.56–6.48 (m, 2H), 6.39–6.35 (m, 1H), 5.85–5.75 (m, 1H), 5.30 (s, 1H), 5.16–5.08 (m, 2H), 4.91–4.77 (m, 2H), 3.70 (s, 3H), 3.67 (s, 3H), 3.22 (t, *J* = 6.6 Hz, 2H), 3.13–3.00 (m, 2H); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$): δ 155.1, 149.2, 148.1, 146.7, 142.8, 135.2, 131.6, 130.4, 129.4, 128.9, 128.4, 123.9, 123.4, 120.9, 117.6, 116.9, 111.8, 111.3, 56.0, 55.9, 51.4, 50.2, 49.7, 35.9; FT-IR (ATR) ν_{max}/cm^{-1} 3287 (N–H), 1617 (C=N), 1290 (N–N=N); HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{24}H_{26}N_9O_2$ 472.2203; Found 472.2213.

***N*-((1-cyclohexyl-1*H*-tetrazol-5-yl)(tetrazolo[1,5-*a*]quinolin-4-yl)methyl)prop-2-yn-1-amine** (**1m**): Pale yellow solid (150.0 mg, 74%, MW) (71.0 mg, 35%, US); mp = 173–174 °C; R_f = 0.22 (Hexanes-AcOEt = 7/3 *v/v*); ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.68 (d, *J* = 8.4 Hz, 1H), 8.28 (s, 1H), 8.01 (d, *J* = 7.9 Hz, 1H), 7.93–7.88 (m, 1H), 7.76–7.72 (m, 1H), 6.17 (s, 1H), 4.99–4.90 (m, 1H), 3.63–3.52 (m, 1H), 2.88 (s, 1H), 2.32 (t, *J* = 2.4 Hz, 1H), 2.26–2.21 (m, 1H), 7.93–7.88 (m, 1H), 2.15–1.94 (m, 5H), 1.84–1.79 (m, 1H), 1.60–1.48 (m, 2H), 1.42–1.32 (m, 1H); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$): δ 153.3, 146.6, 131.6, 131.5, 130.3, 129.4, 128.4, 123.8, 123.3, 116.8, 80.2, 73.3, 58.5, 50.3, 36.4, 33.3, 32.9, 25.4, 25.3, 24.9; FT-IR (ATR) ν_{max}/cm^{-1} 3340 (N-H), 1616 (N=H), 1279 (N-N=N); HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{20}H_{22}N_9$ 388.1992; Found 388.1985.

***N*-benzyl-1-(1-cyclohexyl-1*H*-tetrazol-5-yl)-1-(tetrazolo[1,5-*a*]quinolin-4-yl)methanamine** (**1n**): White solid (140.0 mg, 61%, MW) (73.0 mg, 32%, US); R_f = 0.26 (Hexanes-AcOEt = 7/3 *v/v*); ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.71 (d, *J* = 8.3 Hz, 1H), 8.23 (s, 1H), 8.03 (d, *J* = 7.9 Hz, 1H), 7.95–7.90 (m, 1H), 7.78–7.74 (m, 1H), 7.40–7.26 (m, 5H), 5.82 (s, 1H), 4.64–4.57 (m, 1H), 3.94 (d, *J* = 13.2 Hz, 1H), 3.83 (d, *J* = 13.2 Hz, 1H), 2.10–2.03 (m, 2H), 2.01–

1.93 (m, 3H), 1.92–1.87 (m, 1H), 1.80–1.74 (m, 1H), 1.49–1.40 (m, 1H), 1.39–1.26 (m, 2H); $^{13}C\{^{1}H\}$ NMR (126 MHz, $CDCl_3$): δ 153.7, 146.8, 138.2, 131.5, 131.4, 130.4, 129.4, 128.7, 128.6, 128.5, 128.4, 127.8, 127.3, 123.9, 123.8, 116.8, 58.3, 51.4, 51.0, 33.2, 32.9, 25.3, 25.2, 24.8; FT-IR (ATR) ν_{max}/cm^{-1} 3313 (N-H), 1597 (N=H), 1270 (N-N=N); HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{24}H_{26}N_9$ 440.2305; Found 440.2298.

1-(1-cyclohexyl-1*H*-tetrazol-5-yl)-*N*-(4-methoxybenzyl)-1-(tetrazolo[1,5-*a*]quinolin-4-yl)methanamine (**1o**): Pale yellow solid (141.0 mg, 57%, MW) (73.0 mg, 30%, US); R_f = 0.22 (Hexanes-AcOEt = 7/3 *v/v*); ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.62 (d, *J* = 8.4 Hz, 1H), 8.12 (s, 1H), 7.94 (d, *J* = 7.9 Hz, 1H), 7.85–7.81 (m, 1H), 7.69–7.65 (m, 1H), 7.14 (d, *J* = 8.6 Hz, 1H), 6.79 (d, *J* = 8.6 Hz, 1H), 5.72 (s, 1H), 4.55–4.47 (m, 1H), 3.78 (d, *J* = 13.0 Hz, 1H), 3.72 (s, 3H), 3.66 (d, *J* = 13.0 Hz, 1H), 2.01–1.95 (m, 2H), 1.92–1.78 (m, 2H), 1.59–1.48 (m, 5H), 1.39–1.13 (m, 2H); $^{13}C\{^{1}H\}$ NMR (126 MHz, $CDCl_3$): δ 159.2, 153.7, 146.8, 131.5, 131.3, 130.4, 130.2, 129.7, 129.4, 128.3, 123.9, 116.8, 114.1, 58.3, 55.3, 50.9, 50.7, 33.2, 32.9, 25.3, 25.2, 24.8; FT-IR (ATR) ν_{max}/cm^{-1} 3340 (N-H), 1616 (N=H), 1278 (N-N=N); HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{25}H_{28}N_9O$ 470.2411; Found 470.2400.

***N*-((1-cyclohexyl-1*H*-tetrazol-5-yl)(tetrazolo[1,5-*a*]quinolin-4-yl)methyl)butan-1-amine** (**1p**): White solid (107.0 mg, 51%, MW) (70.0 mg, 33%, US); R_f = 0.39 (Hexanes-AcOEt = 7/3 *v/v*); ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.62–8.68 (m, 1H), 8.11 (s, 1H), 7.95–7.91 (m, 1H), 7.84–7.79 (m, 1H), 7.68–7.63 (m, 1H), 5.79 (s, 1H), 4.79–4.72 (m, 1H), 2.64–2.62 (m, 2H), 2.11–2.04 (m, 1H), 2.03–1.97 (m, 1H), 1.96–1.83 (m, 4H), 1.75–1.69 (m, 1H), 1.50–1.34 (m, 4H), 1.33–1.23 (m, 3H), 0.82 (td, *J* = 7.3, 1.9, 0.8 Hz, 3H); $^{13}C\{^{1}H\}$ NMR (126 MHz, $CDCl_3$): δ 153.9, 146.8, 131.4, 131.2, 130.3, 129.4, 128.3, 124.1, 123.9, 116.8, 58.5, 52.4, 47.6, 33.4, 32.9, 32.0, 25.4, 25.3, 24.9, 20.3, 13.9; FT-IR (ATR) ν_{max}/cm^{-1} 3340 (N-H), 1617 (N=H), 1277 (N-N=N); HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{21}H_{28}N_9$ 406.2462; Found 406.2452.

***N*-((1-cyclohexyl-1*H*-tetrazol-5-yl)(tetrazolo[1,5-*a*]quinolin-4-yl)methyl)cyclohexanamine** (**1q**): Orange oil (93.0 mg, 41%, MW) (58.0 mg, 26%, US); R_f = 0.35 (Hexanes-AcOEt = 7/3 *v/v*); ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.61 (d, *J* = 8.4 Hz, 1H), 8.52 (s, 1H), 7.94 (d, *J* = 7.6 Hz, 1H), 7.84–7.80 (m, 1H), 7.68–7.64 (m, 1H), 5.92 (s, 1H), 4.80–4.73 (m, 1H), 4.47–4.40 (m, 2H), 2.42–2.35 (m, 1H), 2.23–2.17 (m, 5H), 2.12–2.05 (m, 1H), 1.97–1.84 (m, 4H), 1.76–1.69 (m, 4H), 1.47–1.37 (m, 3H), 1.29–1.07 (m, 2H); $^{13}C\{^{1}H\}$ NMR (126 MHz, $CDCl_3$): δ 154.3, 146.8, 140.6, 131.4, 131.0, 130.3, 129.4, 128.3, 124.6, 123.9, 116.8, 58.8, 58.5, 49.2, 33.5, 33.4, 33.1, 33.0, 32.8, 25.8, 25.4, 25.3, 24.9, 24.8; FT-IR (ATR) ν_{max}/cm^{-1} 3340 (N-H), 1617 (N=H), 1276 (N-N=N); HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{23}H_{30}N_9$ 432.2618; Found 432.2611.

1-(1-cyclohexyl-1*H*-tetrazol-5-yl)-*N*-(furan-2-ylmethyl)-1-(tetrazolo[1,5-*a*]quinolin-4-yl)methanamine (**1r**): Red oil (75.0 mg, 33%, MW) (47.7 mg, 21%, US); R_f = 0.22 (Hexanes-AcOEt = 7/3 *v/v*); ^{1}H NMR (500 MHz, $CDCl_3$):

δ 8.61 (d, *J* = 8.3 Hz, 1H), 8.15 (s, 1H), 7.94 (d, *J* = 8.1 Hz, 1H), 7.85–7.81 (m, 1H), 7.69–7.65 (m, 1H), 7.28–7.27 (m, 1H), 6.24–6.22 (m, 1H), 6.13 (d, *J* = 3.1 Hz, 1H), 5.81 (s, 1H), 4.63–4.57 (m, 1H), 3.86 (d, *J* = 14.6 Hz, 1H), 3.77 (d, *J* = 14.6 Hz, 1H), 2.04–1.95 (m, 1H), 1.94–1.81 (m, 4H), 1.73–1.68 (m, 1H), 1.44–1.33 (m, 2H), 1.30–1.22 (m, 1H), 0.86–0.76 (m, 1H); $^{13}C\{^{1}H\}$ NMR (126 MHz, $CDCl_3$): δ 153.5, 151.9, 142.5, 131.5, 131.4, 130.4, 129.4, 128.4, 123.9, 123.6, 116.8, 110.5, 108.5, 58.4, 50.7, 43.9, 33.2, 32.9, 25.3 (2), 24.9; FT-IR (ATR) ν_{max}/cm^{-1} 3340 (N-H), 1616 (N=H), 1278 (N-N=N); HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{22}H_{24}N_9O$ 430.2098; Found 430.2087.

***N*-cyclohexyl-2-(tetrazolo[1,5-*a*]quinolin-4-yl)imidazo[1,2-*a*]pyridin-3-amine** (**8a**): Yellow solid (188.2 mg, 94%, MW) (94.1 mg, 47%, US); mp = 204-206 ºC; R_f = 0.19 (Hexanes-AcOEt = 7/3; *v/v*); ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.52 (s, 1H), 8.19 (d, *J* = 6.9 Hz, 1H), 8.08 (d, *J* = 8.5 Hz, 1H), 7.89 (d, *J* = 8.1 Hz, 1H), 7.80–7.66 (m, 1H), 7.62–7.57 (m, 2H), 7.22–7.18 (m, 1H), 6.88–6.85 (m, 1H), 3.36 (d, *J* = 6.5 Hz, 1H), 2.69 (s, 1H), 1.72–1.66 (m, 2H), 1.60–1.53 (m, 2H), 1.47–1.42 (m, 1H), 1.08–0.99 (m, 4H), 0.95–0.83 (m, 1H); $^{13}C\{^{1}H\}$ NMR (126 MHz, $CDCl_3$): δ 149.0, 147.2, 141.9, 140.8, 133.6, 130.6, 128.6, 128.4, 127.9, 127.3, 127.2, 126.9, 124.2, 123.0, 117.6, 111.9, 56.6, 33.9, 25.6, 24.5; FT-IR (ATR) ν_{max}/cm^{-1} 3274 (N–H), 1632 (C=N); HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{22}H_{21}N_7$ 384.1931; Found 384.1929.

Precursor of compound (**8a**): 2-(2-chloroquinolin-3-yl)-*N*-cyclohexylimidazo[1,2-*a*]pyridin-3-amine (**10a**): Brown oil (125.4 mg, ~100%, MW); R_f = 0.30 (Hexanes-AcOEt = 7/3; *v/v*); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.51 (s, 1H), 8.17– 8.15 (m, 1H), 8.02–7.99 (m, 1H), 7.86–7.83 (m, 1H), 7.73–7.69 (m, 1H), 7.61–7.59 (m, 1H), 7.56–7.51 (m, 1H), 7.20–7.18 (m, 1H), 6.87–6.82 (m, 1H), 3.36 (s, 1H), 2.62 (s, 1H), 1.60 (s, 2H), 1.48 (s, 2H), 1.37 (s, 1H), 0.99–0.93 (m, 3H), 0.82–0.75 (m, 2H); $^{13}C\{^{1}H\}$ NMR (126 MHz, $CDCl_3$) δ 148.7, 147.3, 141.3, 141.1, 130.9, 128.4, 128.1, 127.5, 127.1, 127.0, 125.4, 123.2, 117.1, 112.6, 56.6, 33.9, 25.5, 24.5; FT-IR (ATR) ν_{max}/cm^{-1} 3275 (N–H), 1635 (C=N); HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{22}H_{22}ClN_4$ 377.1527; Found 377.1523.

***N*-(*tert*-butyl)-2-(tetrazolo[1,5-*a*]quinolin-4-yl)imidazo[1,2-*a*]pyridin-3-amine** (**8b**): Yellow solid (172.0 mg, 86%, MW) (110.0 mg, 55%, US); mp = 146-148 ºC; R_f = 0.16 (Hexanes-AcOEt = 7/3; *v/v*); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.58 (s, 1H), 8.37 (d, *J* = 6.9 Hz, 1H), 8.08 (d, *J* = 8.5 Hz, 1H), 7.90 (d, *J* = 8.1 Hz, 1H), 7.79–7.75 (m, 1H), 7.62–7.56 (m, 2H), 7.24–7.20 (m, 1H), 8.87–6.83 (m, 1H), 3.31 (s, 1H), 0.95 (s, 9H); $^{13}C\{^{1}H\}$ NMR (126 MHz, $CDCl_3$): δ 148.7, 147.3, 142.5, 141.0, 136.0, 130.6, 129.5, 128.4, 127.8, 127.5, 127.3, 125.5, 124.7, 123.8, 117.4, 111.7, 55.8, 30.1; FT-IR (ATR) ν_{max} /cm^{-1} 3291 (N–H), 1643 (C=N); HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{20}H_{20}N_7$ 358.1774; Found 358.1766.

***N*-(4-methoxyphenyl)-2-(tetrazolo[1,5-*a*]quinolin-4-yl)imidazo[1,2-*a*]pyridin-3-amine** (**8c**): Yellow solid (168.4 mg, 79%, MW) (93.8 mg, 44%, US); mp = 202-204 ºC; R_f = 0.23 (Hexanes-AcOEt = 3/7; *v/v*); ^{1}H NMR (500 MHz, $CDCl_3$): δ 9.15 (s, 1H), 9.06 (s, 1H), 8.61 (d, *J* = 8.3 Hz, 1H), 8.14 (d, *J* = 8.0 Hz, 1H), 7.98 (d, *J* = 9.2 Hz, 1H), 7.91 (d, *J* = 6.8 Hz, 1H), 7.84–7.80 (m, 1H), 7.70–7.66 (m,1H), 7.52–7.47 (m, 1H), 7.01–6.97 (m, 1H), 6.65 (d, *J* = 8.9 Hz, 2H), 6.47 (d, *J* = 8.9 Hz, 2H), 3.61 (s, 3H); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$): δ 154.6, 145.8, 131.7, 130.1, 130.0, 128.7, 125.7, 124.6, 124.3, 116.9, 116.6, 115.8, 115.1, 55.6; FT-IR (ATR) ν_{max}/cm^{-1} 3285 (N–H), 1632(C=N); HRMS (ESI-TOF) m/z: [M + H]$^+$ Calcd for $C_{23}H_{17}N_7O$ 408.1567; Found 408.1559.

***N*-benzyl-2-(tetrazolo[1,5-*a*]quinolin-4-yl)imidazo[1,2-*a*]pyridin-3-amine** (**8d**): Orange solid (186.0 mg, 91%, MW) (110.4 mg, 54%, US); mp = 113-115 ºC; R_f = 0.12 (Hexanes-AcOEt = 7/3; *v/v*); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.65 (d, *J* = 8.3 Hz, 1H), 8.54 (s, 1H), 8.26 (d, *J* = 6.8 Hz, 1H), 8.01 (d, *J* = 7.9 Hz, 1H), 7.84–7.80 (m, 1H), 7.72–7.68 (m, 1H), 7.59 (d, *J* = 9.0 Hz, 1H), 7.27–7.22 (m, 1H), 6.91–6.84 (m, 5H), 6.78–6.72 (m, 2H), 4.02 (d, *J* = 7.2 Hz, 2H); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$): δ 146.0, 142.5, 138.5, 130.2, 129.9, 129.5, 129.0, 128.3, 128.2, 128.1, 128.0, 127.7, 126.8, 125.1, 124.6, 123.2, 120.1, 117.5, 116.4, 112.0, 52.5; FT-IR (ATR) ν_{max}/cm^{-1} 3267 (N–H), 1674 (C=N); HRMS (ESI-TOF) m/z: [M + H]$^+$ Calcd for $C_{23}H_{17}N_7$ 392.1618; Found 392.1613.

5-bromo-*N*-cyclohexyl-2-(tetrazolo[1,5-*a*]quinolin-4-yl)imidazo[1,2-*a*]pyridin-3-amine (**8e**): Brown oil (178.3 mg, 89%, MW) (146.5 mg, 69%, US); R_f = 0.42 (Hexanes-AcOEt = 3/7; *v/v*); ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.79–8.72 (m, 2H), 8.10 (d, *J* = 7.9 Hz, 1H), 7.90–6.86 (m, 1H), 7.77–7.73 (m, 1H), 7.56 (d, *J* = 8.2 Hz, 1H), 7.06–7.00 (m, 2H), 5.96 (d, *J* = 9.3 Hz, 1H), 2.86–2.80 (m, 1H), 1.85–1.78 (m, 2H), 1.55–1.48 (m, 2H), 1.47–1.41 (m, 1H), 1.08–0.98 (m, 2H), 0.96–0.80 (m, 3H); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$): δ 146.3, 144.5, 132.2, 132.1, 131.5, 130.6, 129.9, 129.3, 128.3, 125.0, 124.6, 120.6, 119.3, 117.1, 116.8, 113.2, 59.9, 32.6, 25.7, 25.3; FT-IR (ATR) ν_{max}/cm^{-1} 3258 (N–H), 1678 (C=N); HRMS (ESI-TOF) m/z: [M + H]$^+$ Calcd for $C_{22}H_{20}BrN_7$ 462.1036; Found 462.1026.

5-bromo-*N*-(4-methoxyphenyl)-2-(tetrazolo[1,5-*a*]quinolin-4-yl)imidazo[1,2-*a*]pyridin-3-amine (**8g**): Yellow oil (171.3 mg, 67%, MW) (79.3 mg, 31%, US); R_f = 0.32 (Hexanes-AcOEt = 7/3; *v/v*); ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.70–8.67 (m, 2H), 8.04 (d, *J* = 8.0 Hz, 1H), 7.88–7.83 (m, 2H), 7.73–7.69 (m, 1H), 7.66 (d, *J* = 8.8 Hz, 1H), 7.16–7.12 (m, 1H), 7.10–7.07 (m, 1H), 6.62 (d, *J* = 9.0 Hz, 2H), 6.35 (d, *J* = 9.0 Hz, 2H), 3.62 (s, 3H); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$): δ 153.3, 145.3, 141.9, 134.1, 132.3,131.1, 130.1, 129.3, 128.3, 126.4, 126.1, 124.4, 119.5, 119.3, 117.1, 116.7, 115.1, 114.7, 113.3, 55.5; FT-IR (ATR) ν_{max}/cm^{-1} 3217 (N–H), 1631 (C=N); HRMS (ESI-TOF) m/z: [M + H]$^+$ Calcd for $C_{23}H_{16}BrN_7O$ 486.0672; Found 486.0655.

***N*-benzyl-5-bromo-2-(tetrazolo[1,5-*a*]quinolin-4-yl)imidazo[1,2-*a*]pyridin-3-amine** (**8h**): Yellow oil (188.3 mg, 77%, MW) (83.1 mg, 34%, US); R_f = 0.27 (Hexanes-AcOEt = 1/1; *v/v*); ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.64 (d, *J* = 8.3 Hz, 1H), 8.28 (s, 1H), 7.96 (d, *J* = 7.9 Hz, 1H), 7.86–7.82 (m, 1H), 7.73–7.68 (m, 1H), 7.58 (d, *J* = 8.6 Hz, 1H), 7.12–7.05 (m, 2H), 6.68–6.57 (m, 5H), 6.48–6.44 (m, 1H), 6.17–6.13 (m, 1H), 4.01 (d, *J* = 6.9 Hz, 2H); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$): δ 145.9, 144.8, 137.7, 133.1, 131.4, 130.5, 129.6, 129.0, 128.5, 128.1, 127.3, 126.5, 125.2, 124.4, 119.8, 119.3, 117.1, 116.4, 113.1, 56.0; FT-IR (ATR) ν_{max}/cm^{-1} 3276 (N–H), 1624 (C=N); HRMS (ESI-TOF) m/z: [M + H]$^+$ Calcd for $C_{23}H_{16}BrN_7$ 470.0723; found 470.0722.

8-(benzyloxy)-*N*-cyclohexyl-2-(tetrazolo[1,5-*a*]quinolin-4-yl)imidazo[1,2-*a*]pyridin-3-amine (**8i**): Yellow oil (186.0 mg, 75%, MW) (146.3 mg, 59%, US); R_f = 0.63 (Hexanes-AcOEt = 7/3; *v/v*); ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.94 (s, 1H), 8.71 (d, *J* = 8.3 Hz, 1H), 8.10 (d, *J* = 7.8 Hz, 1H), 7.84–7.80 (m, 2H), 7.74–7.70 (m, 1H), 7.54 (d, *J* = 7.1 Hz, 2H), 7.43–7.38 (m, 2H), 7.36–7.32 (m, 1H), 6.67–6.63 (m, 1H), 6.52 (d, *J* = 8.9 Hz, 1H), 6.46 (d, *J* = 7.0 Hz, 1H), 5.44 (s, 2H), 2.76–2.68 (m, 1H), 1.80–1.75 (m, 2H), 1.62–1.56 (m, 3H), 1.49–1.43 (m, 1H), 1.28–1.24 (m, 2H), 1.14–1.01 (m, 3H), 0.90–0.82 (m, 1H); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$): δ 147.8, 137.1, 136.5, |135.7, 131.3, 130.9, 130.3, 129.4, 128.8, 128.3, 128.2, 127.3, 125.0, 120.5, 117.0, 116.8, 111.7, 103.0, 101.9, 70.9, 57.1, 34.0, 25.7, 25.3; FT-IR (ATR) ν_{max}/cm^{-1} 3284 (N–H), 1672 (C=N); HRMS (ESI-TOF) m/z: [M + H]$^+$ Calcd for $C_{29}H_{27}N_7O$ 490.2349; Found 490.2344.

8-(benzyloxy)-*N*-(tert-butyl)-2-(tetrazolo[1,5-*a*]quinolin-4-yl)imidazo[1,2-*a*]pyridin-3-amine (**8j**): Yellow solid (130.2 mg, 65%, MW) (56.1 mg, 28%, US); mp = 170-172 ºC; R_f = 0.65 (Hexanes-AcOEt = 7/3; *v/v*); ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.81 (s, 1H), 8.64 (d, *J* = 8.3 Hz, 1H), 8.07–7.97 (m, 2H), 7.80–7.76 (m, 1H), 7.67–7.64 (m, 1H), 7.48–7.45 (m, 2H), 7.34–7.23 (m, 4H), 6.58–6.55 (m, 1H), 6.40 (d, *J* = 7.4 Hz, 1H), 5.33 (s, 2H), 0.85 (s, 9H); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$): δ 147.6, 146.5, 137.6, 136.3, 131.8, 131.7, 130.4, 129.8, 129.4, 129.3, 128.6, 128.2, 128.1, 127.4, 127.3, 124.7, 121.1, 117.7, 116.7, 111.2, 103.1, 70.8, 56.5, 29.5; FT-IR (ATR) ν_{max}/cm^{-1} 3269 (N–H), 1705 (C=N); HRMS (ESI-TOF) m/z: [M + H]$^+$ Calcd for $C_{27}H_{25}N_7O$ 464.2193; Found 464.2203.

***N*-benzyl-8-(benzyloxy)-2-(tetrazolo[1,5-*a*]quinolin-4-yl)imidazo[1,2-*a*]pyridin-3-amine** (**8l**): Yellow solid (179.4 mg, 69%, MW) (83.2 mg, 32%, US); mp = 134-136 ºC; R_f = 0.54 (Hexanes-AcOEt = 1/1; *v/v*); ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.72–8.59 (m, 2H), 8.01 (d, *J* = 7.8 Hz, 1H), 7.90 (d, *J* = 6.72 Hz, 1H), 7.83–7.79 (m, 1H), 7.71–7.67 (m, 1H), 7.56–7.52 (m, 2H), 7.43–7.38 (m, 2H), 7.37–7.32 (m, 1H), 6.86–6.82 (m, 3H), 6.79–6.63 (m, 3H), 6.50 (d, *J* = 7.4 Hz, 1H), 4.00 (d, *J* = 7.2 Hz, 2H); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$): δ 148.0, 146.1, 138.6, 137.3, 136.4, 130.8, 130.2, 129.5, 129.2, 128.8, 128.4, 128.2 (2), 127.8, 127.4, 126.9, 124.8, 120.0, 116.5 (2), 112.0, 103.3, 71.0,

52.7; FT-IR (ATR) ν_{max}/cm^{-1} 3284 (N–H), 1614 (C=N); HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{30}H_{23}N_7O$ 498.2036; Found 498.2031.

4-(dimethoxymethyl)tetrazolo[1,5-*a*]quinoline (**7**): white solid (125.1 mg, ~100%); mp = 138-141 °C; R_f = 0.35 (Hexanes-AcOEt = 7/3; *v/v*); ^1H NMR (500 MHz, $CDCl_3$): δ 8.69 (d, *J* = 8.4 Hz, 1H), 8.15 (s, 1H), 8.03–8.00 (m, 1H), 7.90–7.87 (m, 1H), 7.75–7.71 (m, 1H), 6.03–6.01 (m, 1H), 3.55 (s, 7H); $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$): δ 146.4, 131.3, 130.5, 130.2, 129.5, 128.1, 123.7, 123.5, 116.7, 99.3, 54.3; FT-IR (ATR) ν_{max}/cm^{-1} 1615 (C=N); HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{12}H_{13}N_4O_2$ 245.1033; Found 245.1023.

ASSOCIATED CONTENT

Supporting Information

The supporting Information is available free of charge on the ACS Publications website.

Copies of ^1H and ^{13}C NMR spectra for products **1a-r**, **6b**, **8a-l**, **10a**, and **7** (PDF)

X-ray analysis (ORTEP) for compound **1b**, **6b**, **8a**, and **7** (PDF)

X-ray data for compound **1b**, **6b**, **8a**, and **7** (CIF)

Plausible reaction mechanisms

Computational details

Notes

The authors declare no competing financial interest.

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