



Cite this: *Org. Biomol. Chem.*, 2024, **22**, 5816

Received 5th June 2024,
Accepted 20th June 2024

DOI: 10.1039/d4ob00950a

rsc.li/obc

Leveraging *in situ* *N*-tosylhydrazones as diazo surrogates for efficient access to pyrazolo-[1,5-*c*]quinazolinone derivatives†

Jun Yan,^a Pascal Retailleau,^b Christine Tran^{*a} and Abdallah Hamze ^{*a}

We developed a transition metal-free methodology for the construction of pyrazoloquinazolinone derivatives. The strategy involves a one-pot reaction wherein the *N*-tosylhydrazone and its corresponding diazo derivative are generated *in situ*, followed by an intramolecular 1,3-dipolar cycloaddition–ring expansion to provide the pyrazolo-[1,5-*c*]quinazolinone motif. This approach enables straightforward access to a diverse range of highly functionalized *N*-heterocyclic compounds in good yields (up to 92%).

Introduction

N-Heterocycles have been a focal point for researchers for several decades, particularly due to their diverse pharmaceutical and agrochemical applications.^{1,2} The synthesis of these scaffolds has garnered significant interest among organic chemists, leading to the development of novel synthetic methodologies.^{2–5} Among these structures, pyrazolo-[1,5-*c*]quinazolines, with a *N*-heterocyclic nucleus fusing quinazolines and pyrazoles, have recently emerged as pivotal compounds within the biology and chemistry communities.

These compounds have a range of biological properties, as illustrated in Fig. 1.¹ Specifically, molecules **I** act as antagonists for glycine/NMDA (*N*-methyl-D-aspartic acid) receptors,⁶ as well as for AMPA (α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid) and kainate⁷ receptors, demonstrating high affinities and selectivities toward the corresponding amino acid receptors.^{8,9} Additionally, pyrazolo-[1,5-*c*]quinazolinone derivatives **II** also exhibited comparable activities as antagonists for adenosine receptors.¹⁰

Pyrazolo-[1,5-*c*]quinazolinones **III** emerge as promising antibacterial agents due to their function as DNA gyrase inhibitors.¹¹ Campiani *et al.* reported molecules **IV** as potent reverse transcriptase inhibitor-type antiviral agents.¹² These aza-heterocycles also acted as efficient ligands with high binding affinities towards benzodiazepine and GABA_A

receptors.^{13,14} Through virtual screening, Moro and coworkers identified pyrazolo-[1,5-*c*]quinazolinones **V** as novel casein kinase 2 inhibitors.¹⁵

The Xu group described similar structures with significant antitumor properties and inhibitory activity against cyclin-dependent kinases CDK9 and CDK2.¹⁶ More recently, the photophysical properties of pyrazolo-[1,5-*c*]quinazolines have been scrutinized by Sutherland *et al.*¹⁷ These platforms appeared to be interesting chromophores with high fluorescence quantum yields, paving the way for possible bio-imaging applications.

Alongside the widely diverse properties of pyrazolo-[1,5-*c*]quinazolinones depicted above, numerous synthetic strategies have been explored for constructing this *N*-heterocyclic ring (Scheme 1). One of the earliest methods involves a multi-step

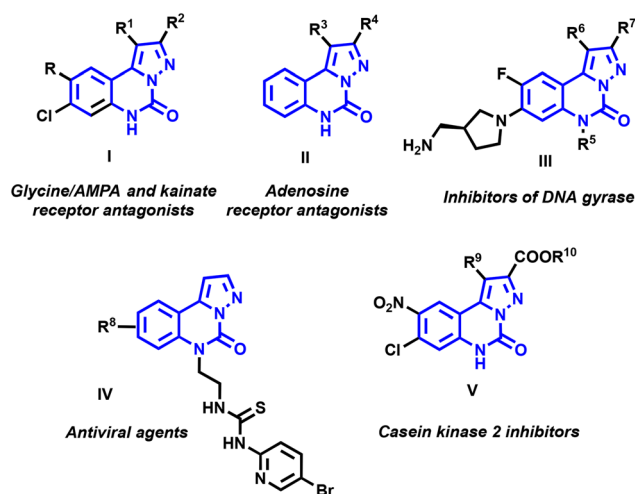


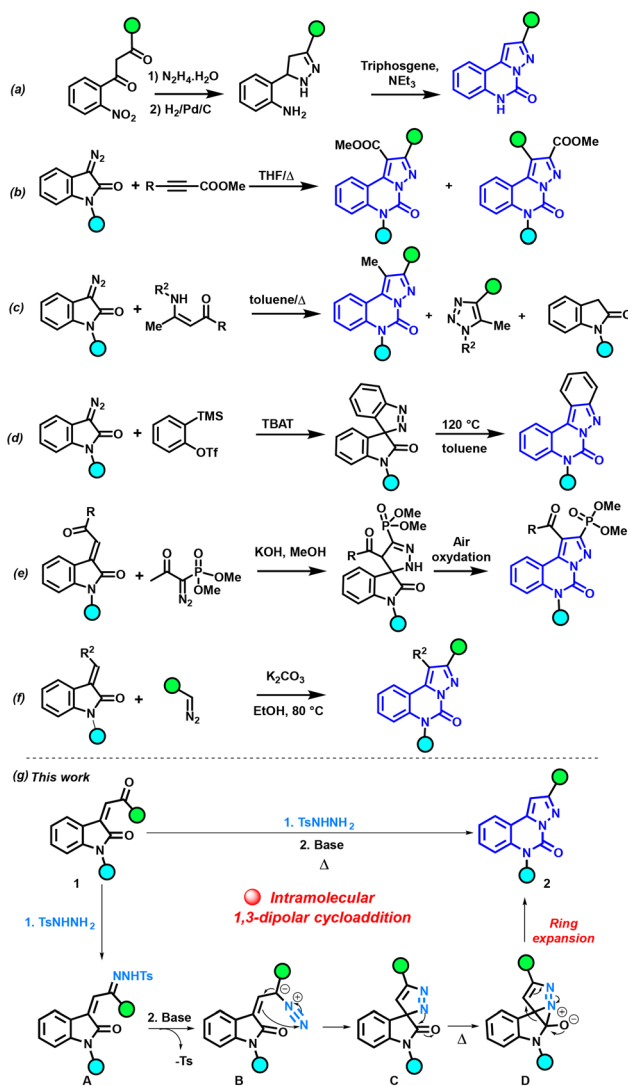
Fig. 1 Biologically active compounds displaying the pyrazolo-[1,5-*c*]quinazolinone scaffold.

^aDepartment of Chemistry and Medicinal Chemistry, Université Paris-Saclay, CNRS, BioCIS, 91400 Orsay, France. E-mail: abdallah.hamze@universite-paris-saclay.fr

^bDepartment of Chemistry and Natural Products, ICSN, Université Paris-Saclay, UPR 2301, 91198 Gif-sur-Yvette, France

† Electronic supplementary information (ESI) available: Experimental procedures, characterization data for new compounds, and crystallographic data. CCDC 2341570 (compound 2a). For ESI and crystallographic data in CIF or other electronic format see DOI: <https://doi.org/10.1039/d4ob00950a>





Scheme 1 Reported approaches for synthesizing pyrazolo-[1,5-c]quinazolinones, and our approach involving intramolecular 1,3-dipolar cycloaddition for their construction.

synthesis, wherein 4,5-dihydro-3,5-diarylpyrazoles are formed by reacting hydrazine hydrate and 1,3-diaryl-2-propenones, and the reaction is completed with a condensation step using triphosgene (Scheme 1a).^{8,10,14,17} Tang and Cao combined 3-diazoindolinones with methyl β -fluoroalkylpropionates to obtain a mixture of two regioisomers of pyrazolo-[1,5-c]quinazolinone (Scheme 1b).^{18,19} Also, a mixture of three compounds was observed when the reaction was performed between diazoindole and enaminones (Scheme 1c).²⁰ Cheng and Zhai developed a [3 + 2] dipolar cycloaddition of arynes with 3-diazoindolin-2-ones in the presence of TBAT (tetrabutylammonium triphenyldifluorosilicate), leading to spiro[indazole-3,3'-indolin]-2'-ones. Their thermal isomerization obtained at 120 °C readily yields indazolo[2,3-c]quinazolin-6 (5*H*)-ones (Scheme 1d).^{21,22} Mohanan *et al.* used the diazo derivative with the Bestmann–Ohira reagent, and the reaction

with an isatin derivative afforded the spiropyrazoline derivative through a 1,3-dipolar cycloaddition followed by a 1,3-*H*-shift, and then a spontaneous air-oxidation in the presence of methanol delivered the phosphonated pyrazolo-[1,5-c]quinazolinones (Scheme 1e).²³ Nagendra Babu *et al.* used a domino reaction with 3-ylideneoxindoles and diazo partners, leading to pyrazoloquinazolinones (Scheme 1f).²⁴

Given our sustained interest in studying the reactivity of *N*-tosylhydrazones (NTHs),^{25–32} we formulated plans to investigate reactions involving these reactive species for the construction of *N*-heterocyclic moieties, specifically the pyrazolo-[1,5-c]quinazolinone scaffold. Within this framework, we conceived an original strategy for pyrazolo-[1,5-c]quinazolinone synthesis through intramolecular cycloaddition (Scheme 1g). Our protocol was conducted under basic conditions and relied on the transition metal-free one-pot reaction between enone **1** and *p*-toluenesulfonyl hydrazide. The initial condensation of **1** with *p*-toluenesulfonyl hydrazide led to the NTH intermediate **A**. Subsequently, under the influence of a base, **A** was converted into the diazo species **B**. **B** then underwent an intramolecular 1,3-dipolar cycloaddition to generate **C**. Through thermal heating, a nucleophilic attack of the azo on the carbonyl group forms the 5/3 fused heterocyclic scaffold **D**.²² The final step involved the ring expansion of **D**, resulting in the formation of the pyrazolo-[1,5-c]quinazolinone **2**.

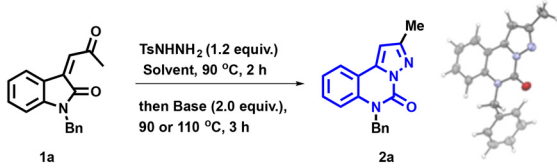
Our approach uniquely relies on *p*-toluenesulfonyl hydrazide for the intramolecular 1,3-dipolar cycloaddition, without the need for any co-substrates. In comparison with prior reports, which are often limited to electron-withdrawing group (EWG)-stabilized diazo compounds, this methodology should be applicable for NTHs with electron-donating groups (EDGs). Additionally, this methodology produces only one regioisomer and eliminates the need for toxic reagents such as triphosgene, providing significant advantages for this reaction.

Results and discussion

We initiated the optimization of the reaction using enone **1a** as the substrate (Table 1). The utilization of a strong base, such as *t*BuLi, resulted in the formation of the desired product **2a**, albeit in a low yield of 18% (Table 1, entry 1). It is worth noting that the structure of **2a** was fully confirmed through X-ray crystal analysis (see the ESI† for further details).³³

Employing a relatively weaker base, LiOtBu, did not result in a significant enhancement in reaction efficiency (entry 2). Subsequently, the exploration continued with an inorganic base such as Cs₂CO₃ (entry 3), which delivered a noteworthy yield of 72%. A further substantial improvement in yield was observed when dioxane was employed, coupled with a switch to K₃PO₄ (entry 4). Compound **2a** was obtained in an excellent NMR yield of 98% and an isolated yield of 92%. Varying the solvent demonstrated the versatility of this transformation in both polar and non-polar solvents (entries 4–6). With a view to improve the sustainability of our system, the green solvent 2-propanol was employed as the reaction medium,³⁴ resulting



Table 1 Reaction optimization^a


Entry	Base	Solvent	¹ HNMR yield (%)	Yield ^b (%)
1	<i>t</i> BuLi	Dioxane	18	n.d. ^c
2	LiO <i>t</i> Bu	Dioxane	20	n.d. ^c
3	Cs ₂ CO ₃	Dioxane	80	72
4	K ₃ PO ₄	Dioxane	98	92
5	K ₃ PO ₄	Toluene	90	85
6	K ₃ PO ₄	2-Propanol	88	80
7	K ₂ CO ₃	Dioxane	92	87
8	K ₃ PO ₄	Dioxane	91 ^d	86

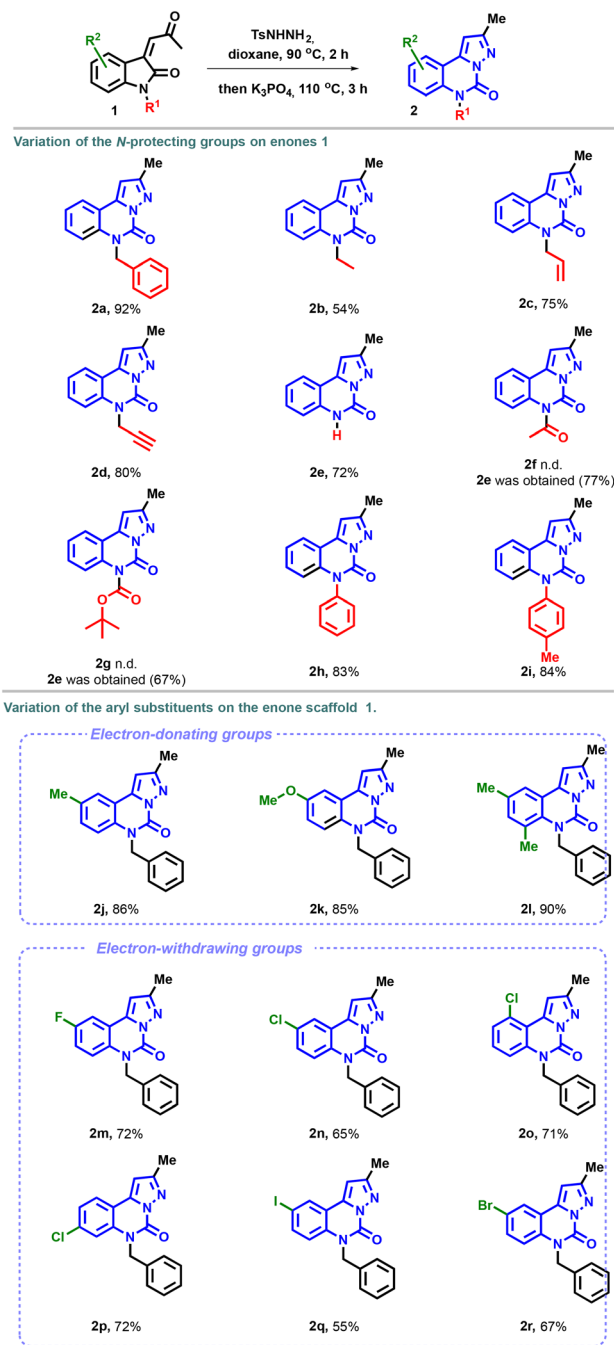
^a Enone **1a** (0.20 mmol, 1.0 equiv.) and *p*-toluenesulfonyl hydrazide (0.24 mmol, 1.2 equiv.) were dissolved in dioxane (2 mL). The reaction was heated in an oil bath at 90 °C and stirred for 2 h. Then, base (0.40 mmol, 2.0 equiv.) was added, and the reaction mixture was stirred at 110 °C for 3 h. ^b Isolated yield after column chromatography. ^c n.d. = not determined. ^d The second step was conducted at 90 °C.

in the corresponding pyrazolo-[1,5-*c*]quinazolinones **2a** in a yield of 80%. Transitioning from K₃PO₄ to K₂CO₃ as the base resulted in a slight decrease in the yield (entry 7). Furthermore, lowering the temperature to 90 °C during the cyclization step led to a marginal decrease in yield to 91% (entry 8).

Consequently, we established the optimal conditions for this transformation, utilizing K₃PO₄ as the base and dioxane as the solvent.

We then began to explore the scope of the reaction. First, we investigated the modification of the amino-protecting groups of enones **1**. As illustrated in Scheme 2, the transformation proved to be well suited for *N*-ethyl-, -allyl-, -propynyl and -phenyl substrates and afforded the corresponding pyrazolo-[1,5-*c*]quinazolinones **2b–i** in good yields. To our satisfaction, the unprotected enone **1e**, under the optimal reaction conditions, provided the desired product **2e** in 72% yield. In contrast, the expected heterocycles **2f** and **2g** with electron withdrawing protecting groups were not detected. Instead, the unprotected compound **2e** was isolated in satisfactory yields (77% and 67% for acetyl and Boc, respectively), possibly due to the basic conditions of the cyclization step.³⁵

Next, the variation of the aryl substituents on the enone scaffold was examined (R² group) (Scheme 2). A good tolerance was observed with methyl and methoxy groups, with yields of 86 and 85%, respectively, for molecules **2j** and **2k**. In particular, the presence of electron-donating substituents promoted the formation of the pyrazolo-[1,5-*c*]quinazolinones **2l**. Similarly, the reaction exhibited good compatibility with diverse electron-poor groups, with yields up to 72%. Higher yields were obtained with fluoro (**2m**), chloro (**2n**), and bromo (**2r**) substituents compared to the results observed with the iodo substituent **2q**. The reaction displayed good efficiency



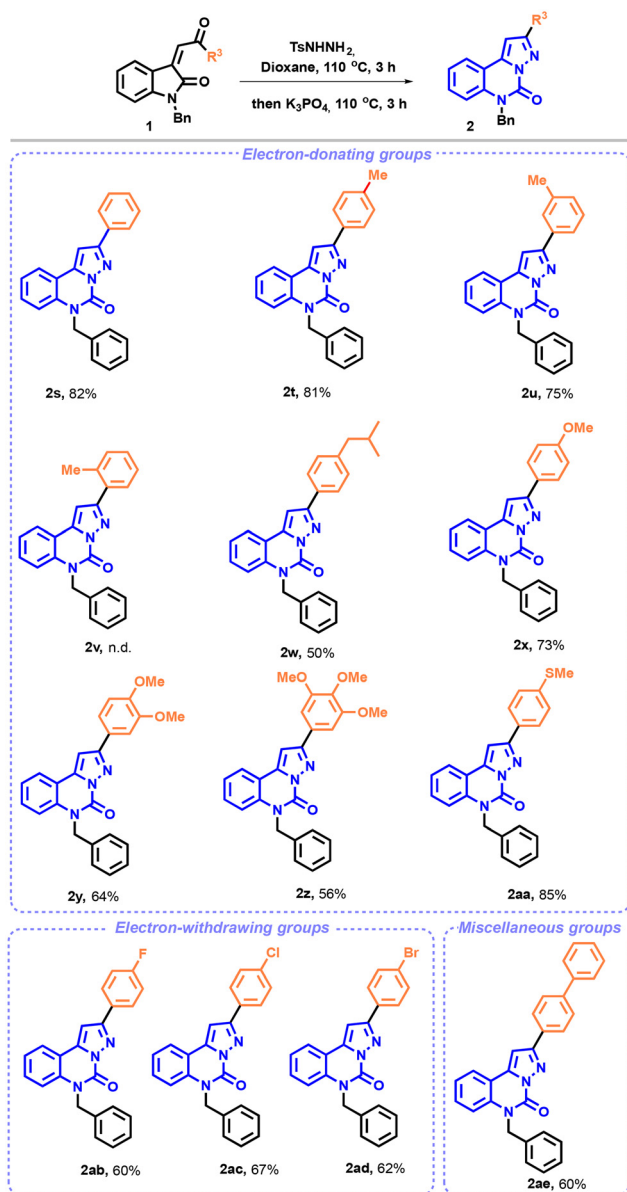
Scheme 2 Substrate scope. ^a Reaction conditions: enone **1** (0.20 mmol, 1.0 equiv.) and *p*-toluenesulfonyl hydrazide (0.24 mmol, 1.2 equiv.) were dissolved in dioxane (2 mL). The reaction was heated in an oil bath at 90 °C, and stirred for 2 h. K₃PO₄ (0.40 mmol, 2.0 equiv.) was then added to the reaction mixture, which was stirred at 110 °C for 3 h. Isolated yield after chromatographic purification.

with *meta*, *ortho*, and *para*-substituted chloroenones, and compounds **2n**, **2o**, and **2p** were obtained in a good yield.

Next, we expanded the scope of our studies by varying the ketone substituents of enones **1** (Scheme 3).

In order to facilitate the formation of the pyrazolo-[1,5-*c*]quinazolinone, we slightly modified the reaction conditions. The

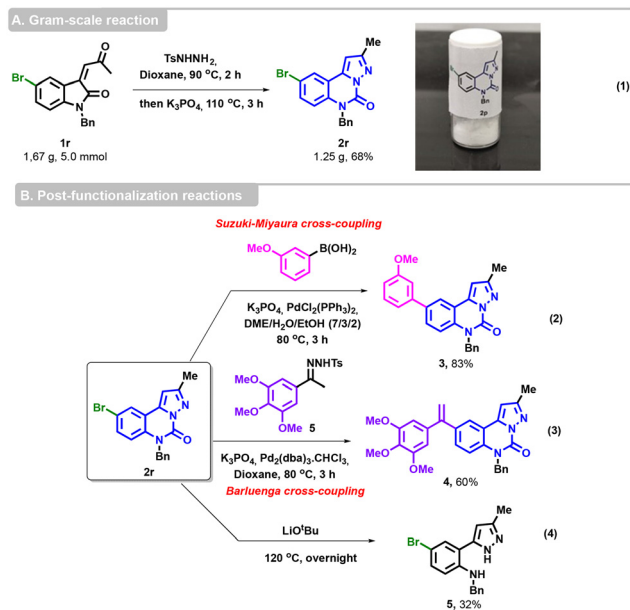




Scheme 3 Substrate scope: variation of the ketone substituents on enones **1**. ^a Reaction conditions: enone **1** (0.20 mmol, 1.0 equiv.) and *p*-toluenesulfonyl hydrazide (0.24 mmol, 1.2 equiv.) were dissolved in dioxane (2 mL). The reaction was heated in an oil bath at 110 °C and stirred for 2 h. K₃PO₄ (0.40 mmol, 2.0 equiv.) was then added to the reaction mixture, which was stirred at 110 °C for 3 h. Isolated yield after chromatographic purification.

NTH synthesis was thus carried out at 110 °C for 3 h, instead of 90 °C for 2 h. Upon first examination, as shown in Scheme 3, the reaction proceeded smoothly with both electron-rich and -poor groups. The phenyl group afforded the desired compound **2s** in 82% yield.

Surprisingly, the effectiveness of the reaction decreased upon the addition of a methyl or an isopropyl substituent to the phenyl moiety. While in the presence of the *para* and *meta*-methylated pyrazolo-[1,5-*c*]quinazolinones the desired compounds (**2t** and **2u**) were obtained in good yields, the *ortho*-



Scheme 4 Gram-scale reaction and post-functionalization reactions.

substituted pyrazolo-[1,5-*c*]quinazolinone **2v** was not isolated under our reaction conditions, probably due to steric hindrance. Only degradation products could be seen on TLC and crude ¹H NMR. Moderate to good yields were achieved with a methoxy or a methylthio group (**2x** and **2aa**) or even in the presence of several electron-donating groups on the phenyl scaffold (**2y** and **2z**). Consistent with the observations made regarding the aryl substituents on substrate **1**, a similar trend was noted for electron-withdrawing substituents, resulting in the formation of compounds **2ab–2ad** in yields ranging from 60 to 67%. Furthermore, we explored a biphenyl substrate, **1ae**, which delivered the expected compound **2ae** in 60% yield.

To confirm the viability of our methodology, we successfully performed a gram-scale reaction with substrate **1r** (5 mmol), delivering the desired cyclized product **2r** in a yield of 68% (1.2 g) (Scheme 4, eqn (1)). Compound **2r** was then subjected to various post-functionalization reactions. A Suzuki–Miyaura cross-coupling was performed with (3-methoxyphenyl)boronic acid, K₃PO₄ as the base and PdCl₂(PPh₃)₂ as the catalyst in DME/H₂O/EtOH³¹ to afford **3** in 83% yield (Scheme 4, eqn (2)).

The Barluenga–Valdés coupling reaction was carried out under the standard conditions between the bromo-derived pyrazoloquinazolinone **2r** and 3,4,5-trimethoxyphenyl NTH **5**, allowing access to the alkene derivative **4** in a satisfactory yield (Scheme 4, eqn (3)). Finally, the hydrolysis of the urea group was also achieved in the presence of LiOtBu at 120 °C, furnishing the expected pyrazole **5** (Scheme 4, eqn (4)).

Conclusions

In summary, the synthesis of pyrazolo-[1,5-*c*]quinazolinone derivatives has been achieved using a convenient methodology.



The process relied on the *in situ* formation of NTH, followed by the generation of the diazo derivative in a basic medium. This intermediate underwent an intramolecular 1,3-dipolar cycloaddition, leading to the expected pyrazolo-[1,5-c]quinazolinones. The wide functional group compatibility (29 diversely functionalized products synthesized in moderate to excellent yields), the transition metal-free process, the bench-stability of substrates, and the step economy of the intramolecular process are significant advantages of this reaction. This one-pot transformation was also validated with the gram-scale synthesis of **2r** in 68% yield. Additionally, various post-functionalization reactions, including pallado-catalyzed cross-couplings, such as the Suzuki–Miyaura and Barluenga–Valdés reactions, were successfully performed with compound **2r**. Further studies are underway to investigate the biological activities of the prepared pyrazolo-[1,5-c]quinazolinones.

Conflicts of interest

The authors declare no conflict of interest.

Acknowledgements

The authors acknowledge the support provided to this project by CNRS, Paris-Saclay University and La Fondation ARC pour la recherche sur le cancer ARCPJA2022060005209. The authors also thank the China Scholarship Council for a fellowship (CSC) to J. Y.

References

- M. Garg, M. Chauhan, P. K. Singh, J. M. Alex and R. Kumar, Pyrazoloquinazolines: Synthetic strategies and bioactivities, *Eur. J. Med. Chem.*, 2015, **97**, 444–461.
- V. K. Singh, A. K. Tiwari and M. Faheem, in *N-Heterocycles: Synthesis and Biological Evaluation*, ed. K. L. Ameta, R. Kant, A. Penoni, A. Maspero and L. Scapinello, Springer Nature Singapore, Singapore, 2022, pp. 313–329, DOI: [10.1007/978-981-19-0832-3_8](https://doi.org/10.1007/978-981-19-0832-3_8).
- Y. Lv, J. Meng, C. Li, X. Wang, Y. Ye and K. Sun, Update on the Synthesis of N-Heterocycles via Cyclization of Hydrazones (2017–2021), *Adv. Synth. Catal.*, 2021, **363**, 5235–5265.
- C.-V. T. Vo and J. W. Bode, Synthesis of Saturated N-Heterocycles, *J. Org. Chem.*, 2014, **79**, 2809–2815.
- W. Guo, M. Zhao, W. Tan, L. Zheng, K. Tao and X. Fan, Developments towards synthesis of N-heterocycles from amidines via C–N/C–C bond formation, *Org. Chem. Front.*, 2019, **6**, 2120–2141.
- F. Varano, D. Catarzi, V. Colotta, F. R. Calabri, O. Lenzi, G. Filacchioni, A. Galli, C. Costagli, F. Deflorian and S. Moro, 1-Substituted pyrazolo[1,5-c]quinazolines as novel Gly/NMDA receptor antagonists: Synthesis, biological evaluation, and molecular modeling study, *Bioorg. Med. Chem.*, 2005, **13**, 5536–5549.
- F. Varano, D. Catarzi, V. Colotta, O. Lenzi, G. Filacchioni, A. Galli and C. Costagli, Novel AMPA and kainate receptor antagonists containing the pyrazolo[1,5-c]quinazoline ring system: Synthesis and structure–activity relationships, *Bioorg. Med. Chem.*, 2008, **16**, 2617–2626.
- F. Varano, D. Catarzi, V. Colotta, G. Filacchioni, A. Galli, C. Costagli and V. Carlà, Synthesis and Biological Evaluation of a New Set of Pyrazolo[1,5-c]quinazoline-2-carboxylates as Novel Excitatory Amino Acid Antagonists, *J. Med. Chem.*, 2002, **45**, 1035–1044.
- F. Varano, D. Catarzi, V. Colotta, D. Poli, G. Filacchioni, A. Galli and C. Costagli, Synthesis and Biological Evaluation of a New Set of Pyrazolo[1,5-c]quinazolines as Glycine/N-Methyl-D-aspartic Acid Receptor Antagonists, *Chem. Pharm. Bull.*, 2009, **57**, 826–829.
- D. Catarzi, V. Colotta, F. Varano, D. Poli, L. Squarzialupi, G. Filacchioni, K. Varani, F. Vincenzi, P. A. Borea, D. Dal Ben, C. Lambertucci and G. Cristalli, Pyrazolo[1,5-c]quinazoline derivatives and their simplified analogues as adenosine receptor antagonists: Synthesis, structure–affinity relationships and molecular modeling studies, *Bioorg. Med. Chem.*, 2013, **21**, 283–294.
- A. L. Aguirre, P. R. Chheda, S. R. C. Lentz, H. A. Held, N. P. Groves, H. Hiasa and R. J. Kerns, Identification of an ethyl 5,6-dihydropyrazolo[1,5-c]quinazoline-1-carboxylate as a catalytic inhibitor of DNA gyrase, *Bioorg. Med. Chem.*, 2020, **28**, 115439.
- G. Campiani, F. Aiello, M. Fabbrini, E. Morelli, A. Ramunno, S. Armaroli, V. Nacci, A. Garofalo, G. Greco, E. Novellino, G. Maga, S. Spadari, A. Bergamini, L. Ventura, B. Bongiovanni, M. Capozzi, F. Bolacchi, S. Marini, M. Coletta, G. Guiso and S. Caccia, Quinoxalinyethylpyridylthioureas (QXPTs) as Potent Non-Nucleoside HIV-1 Reverse Transcriptase (RT) Inhibitors. Further SAR Studies and Identification of a Novel Orally Bioavailable Hydrazine-Based Antiviral Agent, *J. Med. Chem.*, 2001, **44**, 305–315.
- G. Guerrini, G. Ciciani, S. Ciattini, L. Crocetti, S. Daniele, C. Martini, F. Melani, C. Vergelli and M. P. Giovannoni, Pyrazolo[1,5-a]quinazoline scaffold as 5-deaza analogue of pyrazolo[5,1-c][1,2,4]benzotriazine system: synthesis of new derivatives, biological activity on GABAA receptor subtype and molecular dynamic study, *J. Enzyme Inhib. Med. Chem.*, 2016, **31**, 195–204.
- V. Colotta, D. Catarzi, F. Varano, G. Filacchioni, L. Cecchi, A. Galli and C. Costagli, Synthesis and Binding Activity of Some Pyrazolo[1,5-c]quinazolines as Tools To Verify an Optional Binding Site of a Benzodiazepine Receptor Ligand, *J. Med. Chem.*, 1996, **39**, 2915–2921.
- S. Moro, F. Varano, G. Cozza, M. A. Pagano, G. Zagotto, A. Chilin, A. Guiotto, D. Catarzi, V. Calotta and L. A. Pinna, Pyrazoloquinazoline Tricyclic System as Novel Scaffold to Design New Kinase CK2 Inhibitors, *Lett. Drug Des. Discovery*, 2006, **3**, 281–284.



- 16 D. Zheng, C. Yang, X. Li, D. Liu, Y. Wang, X. Wang, X. Zhang, Y. Tan, Y. Zhang, Y. Li and J. Xu, Design, Synthesis, Antitumour Evaluation, and In Silico Studies of Pyrazolo-[1,5-c]quinazolinone Derivatives Targeting Potential Cyclin-Dependent Kinases, *Molecules*, 2023, **28**, 6606.
- 17 J. D. Bell, A. H. Harkiss, D. Nobis, E. Malcolm, A. Knuhtsen, C. R. Wellaway, A. G. Jamieson, S. W. Magennis and A. Sutherland, Conformationally rigid pyrazoloquinazoline α -amino acids: one- and two-photon induced fluorescence, *Chem. Commun.*, 2020, **56**, 1887–1890.
- 18 L.-Y. Qiu, N. Ren, Z. Deng, J. Chen, H. Deng, H. Zhang, W. Cao and X.-J. Tang, The Practical Access to Fluoroalkylated Pyrazolo[1,5-c]quinazolines by Fluoroalkyl-Promoted [3 + 2] Cycloaddition Reaction, *J. Org. Chem.*, 2023, **88**, 10180–10189.
- 19 Q. Chen, K. Li, T. Lu and Q. Zhou, Phosphine-catalyzed domino reactions of alkynyl ketones with sulfonylhydrazones: construction of diverse pyrazoloquinazoline derivatives, *RSC Adv.*, 2016, **6**, 24792–24796.
- 20 R. Augusti and C. Kascheres, Reactions of 3-diazo-1,3-dihydro-2H-indol-2-one derivatives with enaminones. A novel synthesis of 1,2,3-triazoles, *J. Org. Chem.*, 1993, **58**, 7079–7083.
- 21 B. Cheng, B. Zu, B. Bao, Y. Li, R. Wang and H. Zhai, Synthesis of Spiro[indazole-3,3'-indolin]-2'-ones via [3 + 2] Dipolar Cycloaddition of Arynes with 3-Diazoindolin-2-ones and Indazolo[2,3-c]quinazolin-6(5H)-ones by Subsequent Thermal Isomerization, *J. Org. Chem.*, 2017, **82**, 8228–8233.
- 22 B. Cheng, Y. Li, B. Zu, T. Wang, R. Wang, Y. Li and H. Zhai, Syntheses of spiro[indazole-3,3'-indolin]-2'-ones and spiro[indazole-3,3'-indolin]-2'-imines via 1,3-dipolar cycloadditions of aryne and studies on their isomerization reactions, *Tetrahedron*, 2019, **75**, 130775.
- 23 A. K. Gupta, S. Ahamad, E. Gupta, R. Kant and K. Mohanan, Substrate-controlled product-selectivity in the reaction of the Bestmann–Ohira reagent with N-unprotected isatin-derived olefins, *Org. Biomol. Chem.*, 2015, **13**, 9783–9788.
- 24 G. Ramu, N. Hari Krishna, G. Pawar, K. N. Visweswara Sastry, J. B. Nanubolu and B. Nagendra Babu, Solvent-Controlled, Tunable Domino Reaction of 3-Ylideneoxindoles with in Situ-Generated α -Aryldiazomethanes: A Facile Access to 3-Spirocyclopropyl-2-oxindole and Pyrazoloquinazolinone Scaffolds, *ACS Omega*, 2018, **3**, 12349–12360.
- 25 A. Hamze, B. Tréguier, J.-D. Brion and M. Alami, Copper-catalyzed reductive coupling of tosylhydrazones with amines: A convenient route to α -branched amines, *Org. Biomol. Chem.*, 2011, **9**, 6200–6204.
- 26 J. Aziz, J.-D. Brion, A. Hamze and M. Alami, Copper Acetoacetate [Cu(acac)₂]/BINAP-Promoted Csp³=N Bond Formation via Reductive Coupling of N-Tosylhydrazones with Anilines, *Adv. Synth. Catal.*, 2013, **355**, 2417–2429.
- 27 M. Roche, J. Bignon, J.-D. Brion, A. Hamze and M. Alami, Tandem One-Pot Palladium-Catalyzed Coupling of Hydrazones, Haloindoles, and Amines: Synthesis of Amino-N-vinylindoles and Their Effect on Human Colon Carcinoma Cells, *J. Org. Chem.*, 2014, **79**, 7583–7592.
- 28 K. Zhang, O. Provot, C. Tran, M. Alami and A. Hamze, Copper-catalyzed sulfonylation of N-tosylhydrazones followed by a one-pot C–N bond formation, *Org. Biomol. Chem.*, 2021, **19**, 5358–5367.
- 29 K. Zhang, O. Provot, M. Alami, C. Tran and A. Hamze, Pd-Catalyzed Coupling of N-Tosylhydrazones with Benzylic Phosphates: Toward the Synthesis of Di- or Tri-Substituted Alkenes, *J. Org. Chem.*, 2022, **87**, 1249–1261.
- 30 J. Yan, C. Tran, J. Bignon, O. Provot and A. Hamze, Synthesis of Dihydro-5H-Benzo[c]-Fluorenes, Dihydroindeno[c]-Chromenes and Thiochromenes via Intramolecular Cyclization and their Effect on Human Leukemia Cells, *Adv. Synth. Catal.*, 2022, **364**, 1613–1619.
- 31 J. Yan, C. Tran, P. Retailleau, M. Alami and A. Hamze, Catalyst-Free Synthesis of Functionalized 4-Substituted-4H-Benzo[d][1,3]oxazines via Intramolecular Cyclization of ortho-Amide-N-tosylhydrazones, *J. Org. Chem.*, 2023, **88**, 8636–8642.
- 32 X. Liu, O. Provot, R. Franco, P. Retailleau, M. Alami, V. Gandon, C. Tran and A. Hamze, Synthesis of Aza-Heterocyclic Compounds with N-Tosylhydrazones: Formation of Bi-Indoles via Reductive Molybdenum Catalysis, *Adv. Synth. Catal.*, 2023, **365**, 3155–3161.
- 33 CCDC 2341570 (**2a**)[†] contains the supporting crystallographic data for this paper.
- 34 K. Alfonsi, J. Colberg, P. J. Dunn, T. Fevig, S. Jennings, T. A. Johnson, H. P. Kleine, C. Knight, M. A. Nagy, D. A. Perry and M. Stefaniak, Green chemistry tools to influence a medicinal chemistry and research chemistry based organisation, *Green Chem.*, 2008, **10**, 31–36.
- 35 S. R. Dandepally and A. L. Williams, Microwave-assisted N-Boc deprotection under mild basic conditions using K₃PO₄·H₂O in MeOH, *Tetrahedron Lett.*, 2009, **50**, 1071–1074.

