chemistry proceedings

MDPI

Proceeding Paper

Synthesis of Imidazo[1,2-a]pyridine-Chromones via Groebke-Blackburn-Bienayme Reaction †

Alejandro Corona-Díaz, David Calderón-Rangel, Pedro A. Cano, Cristian Saldaña Arredondo and Rocío Gámez-Montaño *

Departamento de Química, Universidad de Guanajuato, Noria Alta S/N, Col. Noria Alta, Guanajuato 36050, Mexico

* Correspondence: rociogm@ugto.mx; Tel.:+52-473-732-0006 (ext. 8191)

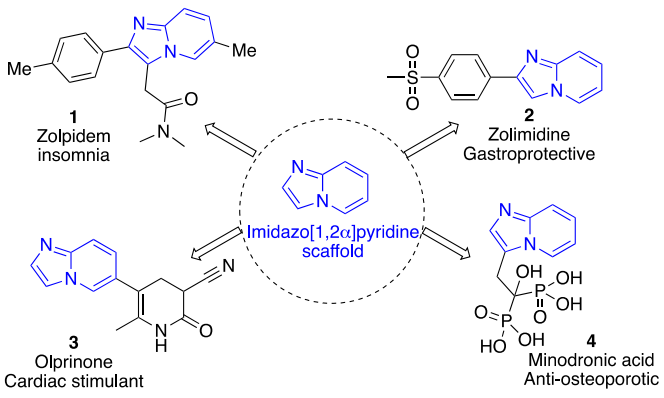
† Presented at the 28th International Electronic Conference on Synthetic Organic Chemistry (ECSOC 2024), 15–30 November 2024; Available online: https://sciforum.net/event/ecsoc-28.

Abstract: The synthesis of Imidazo[1,2-α]pyridines (IMPs), via Multicomponent Reactions based in Isocyanides (I-MCR) offers several advantages over multistep and/or conventional syntheses. The Groebke-Blackburn-Bienaymé (GBB) reaction is the method of choice for synthesizing imidazole analogs. Although IMPs are privileged drug-scaffolds, however, their syntheses often require numerous reagents, high temperatures, long reaction times, and overall low yields. The GBB synthesis of IMPs contain heterocyclic cores using inexpensive reagents in room temperature, has been little reported. In the present work, we describe the synthesis of analogues of IMPs functionalized with a chromone moiety in the imidazole ring, which is documented in the design of materials with fluorescent properties.

Keywords: isocyanide-based multicomponent reactions (I-MCRs); chromone; GBB; IMPs

1. Introduction

Multicomponent reactions (MCRs) are powerful tools for efficiently synthesizing libraries of diverse, complex molecules, with high efficiency and with a green approach. The Groebke-Blackburn-Bienaymé reaction [1,2] discovered independently by Katrin Groebke in Switzerland, Christopher Blackburn in USA and Hugues Bienaymé in France, is one of the most common methodologies for synthesizing imidazo[1,2α]pyridines in highly yields. Imidazo[1,2-α]pyridines (IMPs) are considered a privileged scaffolds in medicinal chemistry due the broad spectrum of pharmaceutical and biological applications [3]. Many commercial drugs, such as Zolpidem (**1**), Olprinone (**3**) and Minodronic acid (**4**) contain an imidazo[1,2α]pyridine core (Figure 1). Other biological activities associate with this core include tubulin inhibitor [4], PI3K inhibitor [5] and mycobacterial inhibition [6].



Citation: Corona-Díaz, A.; Calderón-Rangel, D.; Cano, P.A.; Arredondo, C.S.; Gámez-Montaño, R. Synthesis of Imidazo[1,2-a]pyridine-Chromones via Groebke-Blackburn-Bienayme Reaction. *Chem. Proc.* **2024**, *6*, x. https://doi.org/10.3390/xxxxx

Academic Editor(s): Name

Published: 15 November 2024

Figure 1. Commercially imidazo[1,2-*a*]pyridine drugs.

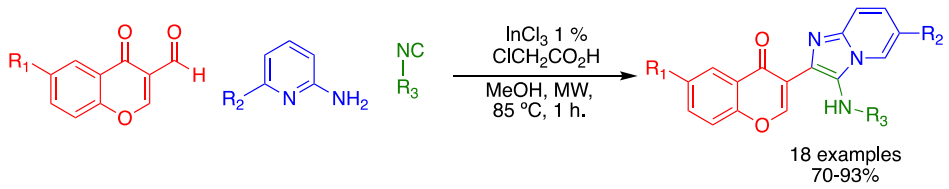
On the other hand, chromone is present in natural products, this core is of great interest in medicinal chemistry and is present in various bioactive compounds, their structure can be modified by attaching different substituents to the benzene or pyrone ring [7].

2. Results and Discussion

Following our main research focus on the design and development of efficient I-MCR based strategies for the synthesis of compounds of interest [8–13], as well the synthesis of IMPs [14–16], and in continuation of our work reported in 2015, which corresponded to the first synthesis of IMPs with a Chromone moiety, via GBB reaction and microwave irradiation (Scheme 1) [17]. Here, we present the synthesis of five IMP incorporating a chromone moiety, in 6 h of reaction and yield of 60–66% (Scheme 1).

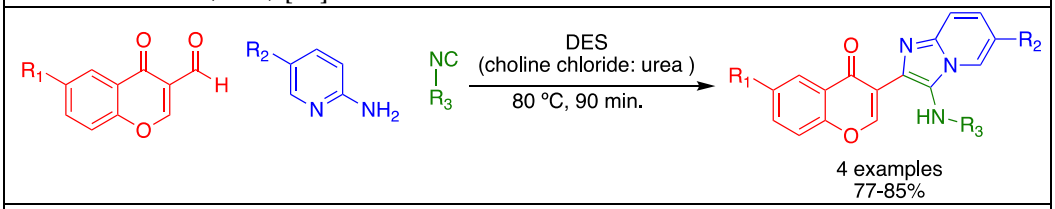
PREVIOUS WORK

Gámez Montaño R. et al. (2015) [17].



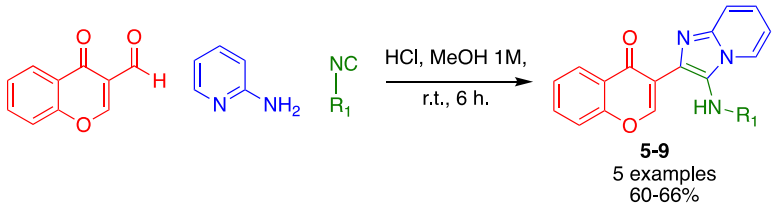
R_1= H, F
R_2= H, Br
R_3= *tert*-butyl, *c*-Hex, Bn, 4-OMeBn, 3,4-OMePhEt

Shabanni et al. (2015) [18]



R_1 = Cl, Me
R_2 = H, Br
R_3 = *tert*-butyl, *c*-Hex, Tos

This work



R_1 = *tert*-butyl, *c*-Hex, Bn, 4-OMeBn, 3,4-OMePhEt

Scheme 1. Previous reports of IMPs with chromone fragment and this work.

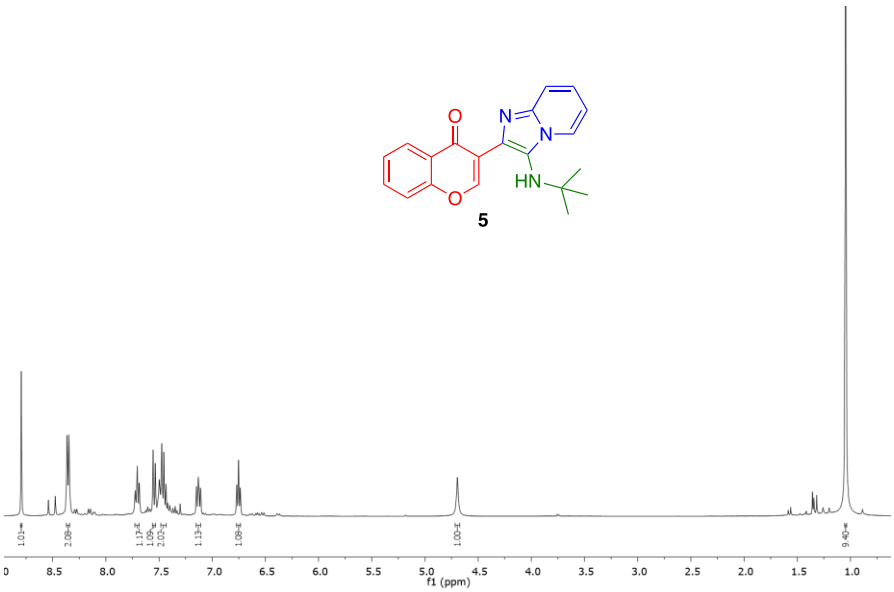


Figure 2. ^{1}H NMR spectrum of compound **5**.

3. Experimental Section

3.1. General Information, Instrumentation and Chemicals

Commercially available starting materials were purchased from Sigma–Aldrich and were used without further purification. IR spectra were recorded on a Perkin Elmer 100 FT-IR spectrometer (ν in cm^{-1}). ^{1}H and ^{13}C NMR spectra were acquired in Bruker (500 MHz) spectrometers. $CDCl_3$ was used as solvent and chemical shifts were reported in ppm. Coupling constants were reported in Hz. Internal reference for ^{1}H NMR spectra is respect to TMS at 0.0 ppm. Internal reference for ^{13}C NMR spectra is respect to $CDCl_3$ at 77.00 ppm. HRMS spectra were acquired via electrospray ionization ESI (+) and recorded via the TOF method. Melting points were determined on a Fisher–Johns apparatus and are uncorrected. The reaction progress was monitored by TLC, and the spots were visualized under UV light (254 or 365 nm)

3.2. General Procedure

General procedure (GP): In a sealed CEM DiscoverTM microwave reaction tube with 10 mL capacity, the aldehyde (1.0 equiv.) in methanol, aminopyridine (1.0 equiv.), isocyanide (1.0 equiv.), HCl (1.0 equiv.) were sequentially added. The reaction mixture was stirred at room temperature for 6 h. The residue was purified by flash chromatography to afford the corresponding imidazo[1,2-a]pyridine (**5–9**).

3.3. Spectral Data

3.3.1. Synthesis and Characterization of the 3-(3-(tert-butylamino)imidazo[1,2-*α*]pyridin-2-yl)-4H-chromen-4-one (**5**) [17]

According to the GP, 3-formylchromone (20 mg, 0.11 mmol), 2-aminopyridine (10.8 mg, 0.11 mmol) and tert-butyl isocyanide (14.3 µL, 0.11 mmol), MeOH (1 M), HCl (9.5 µL, 0.11 mmol), to afford the compound **5** (25 mg, 65%) as pale yellow solid, Rf = 0.4 (Hexanes-AcOEt = 1:1 *V*/*V*); FT-IR (ATR)ν_{max}/cm^{-1}: 3280, 2926, 1627, 1138; ^{1}H NMR (500 MHz, $CDCl_3$,): δ 8.80 (s, 1 H), 8.35 (d, J = 7.0 Hz, 2 H), 7.72–7.66 (m, 1 H), 7.55 (d, J = 8.4 Hz, 1 H), 7.51–7.42 (m, 2 H), 7.16–7.10 (m, 1 H), 6.78–6.73 (m, 1 H), 4.71 (1 H), 1.05 (s, 9 H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 176.7, 156.6, 156.4, 142.7, 133.9, 130.4, 128.2, 126.5, 125.5, 124.4, 124.3, 124.1, 121.6, 118.1, 116.9, 111.0, 56.0, 29.3; HRMS (ESI+): *m*/*z* calcd. for $C_{20}H_{20}N_3O_2^+$ 334.1556, found 334.1553.

3.3.2. Synthesis and Characterization of the 3-(3-(cyclohexylamino)imidazo[1,2-α]pyridin-2-yl)-4H-chromen-4-one (**6**) [17]

According to the GP, 3-formylchromone (20 mg, 0.11 mmol), 2-aminopyridine (10.8 mg, 0.11 mmol) and cyclohexylisocyanide (0.11 mmol) MeOH (1 M), HCl (9.5 μL, 0.11 mmol), to afford the compound **6** (27 mg, 65%) as a brown solid; mp = 142 °C; Rf = 0.15 (Hexanes-AcOEt = 7/3 *V*/*V*); FT-IR (ATR)ν_{max}/cm^{-1}:3278, 2920, 1629, 1143; ^{1}H NMR (500 MHz; $CDCl_3$; 25 °C; TMS): δ 8.82 (s, 1 H), 8.37 (dd, J = 8.0, 1.5 Hz, 1 H), 8.12 (dt, J = 6.9, 1.2 Hz, 1H), 7.75–7.70 (m, 1 H), 7.56 (dd, J = 8.4, 0.6 Hz, 1 H), 7.51–7.44 (m, 2 H), 7.15–7.10 (m, 1 H), 6.81–6.75 (m, 1 H), 5.17 (d, J = 9.1 Hz, 1 H), 2.72–2.61 (m, 1 H), 1.83 (d, J = 9.3 Hz, 2 H), 1.66 (d, J = 5.2 Hz, 2 H), 1.51 (d, J = 5.9 Hz, 1 H), 1.19–1.06 (m, 5 H); ^{13}C NMR (125 MHz, $CDCl_3$; 25 °C; TMS): δ 177.3, 156.8, 156.7, 142.4, 134.1, 129.9, 127.6, 126.8, 125.8, 124.6, 124.2, 123.5, 121.1, 118.6, 117.4, 111.6, 56.6, 34.0, 25.5, 25.0; HRMS (ESI+): *m*/*z* calcd. for $C_{22}H_{22}N_3O_2^+$ 360.1712, found 360.1737.

3.3.3. Synthesis and Characterization of the 3-(3-(benzylamino)imidazo[1,2-α]pyridin-2-yl)-4H-chromen-4-one (**7**) [17]

According to the GP, 3-formylchromone (20 mg, 0.11 mmol), 2-aminopyridine (10.8 mg, 0.11 mmol) and benzylisocyanide (0.11 mmol), MeOH (1 M), HCl (9.5 μL, 0.11 mmol), to afford the compound **7** (28.0 mg, 66%) as an orange solid; mp = 124 °C; Rf = 0.12 (Hexanes-AcOEt = 7/3 *V*/*V*); FT-IR (ATR)ν_{max}/cm^{-1}: 3289, 2836, 1629, 1148; ^{1}H NMR (500 MHz; $CDCl_3$; 25 °C; TMS): δ 8.45 (s, 1 H), 8.28 (d, J = 8.0 Hz, 1 H), 8.17 (d, J = 6.8 Hz, 1 H), 7.72–7.67 (m, 1 H), 7.49 (d, J = 8.2 Hz, 2 H), 7.46–7.42 (m, J = 7.5 Hz, 1 H), 7.17–7.12 (m, 1 H), 7.00–6.94 (m, 5 H), 6.82–6.78 (m, 1 H), 5.48 (t, J = 7.2 Hz, 1H), 3.99 (d, J = 7.1 Hz, 2H); 13C NMR (125 MHz, $CDCl_3$; 25 °C; TMS): δ 176.3, 156.0, 142.2, 139.4, 133.7, 129.1, 128.7, 128.2, 128.0, 127.0, 126.3, 125.4, 124.2, 124.0, 122.7, 120.1, 118.1, 117.3, 111.7, 52.5; HRMS (ESI+): *m*/*z* calcd. for $C_{23}H_{18}N_3O_2^+$ 368.1399, found 368.1401.

3.3.4. Synthesis and Characterization of the 3-(3-((4-methoxybenzyl)amino)imidazo[1,2-α]pyridin-2-yl)-4H-chromen-4-one (**8**) [17]

According to the GP, 3-formylchromone (20 mg, 0.11 mmol), 2-aminopyridine (10.8 mg, 0.11 mmol) and 4-methoxybenzylisocyanide (0.11 mmol), MeOH (1 M), HCl (9.5 μL, 0.11 mmol), to afford the compound **8** (30 mg, 66%) as an orange solid; mp = 190 °C; Rf = 0.11 (Hexanes-AcOEt = 7/3 *V*/*V*); FT-IR (ATR)ν_{max}/cm^{-1}: 3295, 2932, 1629, 1461; 1H NMR (500 MHz; $CDCl_3$; 25 °C; TMS): δ 8.29 (s, 1 H), 7.79 (dd, J = 8.2, 2.8 Hz, 1 H), 7.65–7.60 (m, 1 H), 7.47–7.34 (m, 3 H), 7.13–7.05 (m, 2 H), 6.63 (d, J = 8.3 Hz, 2 H), 6.25 (d, J = 8.3 Hz, 2 H), 4.77 (bs, 1 H), 3.90 (s, 2 H), 3.47 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$; 25 °C; TMS): δ 174.8, 161.1, 158.8, 158.6, 157.0, 151.8, 130.4, 130.3, 126.7, 125.3, 122.4, 122.2, 120.5, 120.4, 120.3, 115.6, 113.4, 111.1, 110.9, 55.3, 55.1; HRMS (ESI+): *m*/*z* calcd. for $C_{24}H_{20}N_3O_3^+$ 398.1505, found 398.1505.

3.3.5. 3-(3-((3,4-dimethoxyphenethyl)amino)imidazo[1,2-α]pyridin-2-yl)-4H-chromen-4-one (**9**) [17]

According to the GP, 3-formylchromone (20 mg, 0.11 mmol), 2-aminopyridine (10.8 mg, 0.11 mmol) and 3,4-dimethoxyphenethylisocyanide (0.11 mmol) MeOH (1 M), HCl (9.5 μL, 0.11 mmol), to afford the compound **9** (29.5 mg, 60%) as a pale yellow oil; Rf = 0.10 (Hexanes-AcOEt = 7/3 *V*/*V*); FT-IR (ATR)ν_{max}/cm^{-1}: 3281, 2926, 1629, 1138; 1H NMR (500 MHz; $CDCl_3$; 25 °C; TMS): δ 8.77 (s, 1 H), 8.26 (d, J = 7.9 Hz, 1 H), 7.95 (d, J = 6.9 Hz, 1 H), 7.74–7.68 (m, 1 H), 7.54 (d, J = 8.4 Hz, 1 H), 7.50–7.43 (m, 2 H), 7.15–7.09 (m, 1 H), 6.77–6.72 (m, 1 H), 6.65–6.60 (m, 3 H), 5.44 (t, J = 7.0 Hz, 1 H), 3.78 (s, 3 H), 3.75 (s, 3 H), 3.19 (q, J = 7.0 Hz, 2 H), 2.71 (t, J = 7.1 Hz, 2 H); ^{13}C NMR (125 MHz, CDCl3; 25 °C; TMS): δ 176.3, 156.1, 156.0, 148.8, 147.4, 141.9, 133.8, 131.9, 130.2, 126.4, 126.3, 125.5, 124.2, 123.9, 122.9, 120.7, 120.5, 118.3, 117.2, 112.0, 111.5, 111.1, 55.8, 49.2, 36.4; HRMS (ESI+): *m*/*z* calcd. for $C_{24}H_{20}N_3O_3^+$: 442.1767, found 442.1798.

4. Conclusions

The contributions impact in several fields, like green chemistry, multicomponent one-pot processes, and in the design of drug-scaffolds GBB products. This work presents the synthesis of imidazo[1,2-a]pyridin-2-yl)-4H-chromen-4-one, via GBB reaction, under room temperature. The main advantages of the protocol are; eco-friendly, inexpensive, and easily accessible reagents and green solvent.

Author Contributions: All authors contributed equally to this work. All authors have read and agreed to the published version of the manuscript.

Funding: This research was funded by DAIP-UG 066-2024 project.

Institutional Review Board Statement: Not applicable.

Informed Consent Statement: Not applicable.

Data Availability Statement:

Acknowledgments: A.C.-D. (490344/2907767), D.C.-R. (666925/2782364), and R.G.M. thanks CONAHCYT-México for a scholarship and Laboratorio Nacional de Caracterizacion de Propiedades Fisicoquímicas y Estructura Molecular (CONACYT-México, Project: 123732).

Conflicts of Interest: The authors declare no conflicts of interest.

References

1. Boltjes, A.; Dömling, A. The Groebke-Blackburn-Bienaymé Reaction. *Eur. J. Org. Chem.* **2019**, *2019*, 7007–7049. https://doi.org/10.1002/ejoc.201901124.
2. Devi, N.; Rawal, R.K.; Singh, V. Diversity-Oriented Synthesis of Fused-Imidazole Derivatives via Groebke–Blackburn–Bienayme Reaction: A Review. *Tetrahedron* **2015**, *71*, 183–232. https://doi.org/10.1016/j.tet.2014.10.032.
3. Vanda, D.; Zajdel, P.; Soural, M. Imidazopyridine-Based Selective and Multifunctional Ligands of Biological Targets Associated with Psychiatric and Neurodegenerative Diseases. *Eur. J. Med. Chem.* **2019**, *181*, 111569. https://doi.org/10.1016/j.ejmech.2019.111569.
4. Sayeed, I.B.; Lakshma Nayak, V.; Shareef, M.A.; Chouhan, N.K.; Kamal, A. Design, Synthesis and Biological Evaluation of Imidazopyridine–Propenone Conjugates as Potent Tubulin Inhibitors. *Med. Chem. Commun.* **2017**, *8*, 1000–1006. https://doi.org/10.1039/C7MD00043J.
5. Lee, H.; Kim, S.J.; Jung, K.H.; Son, M.K.; Yan, H.H.; Hong, S.; Hong, S.-S. A Novel Imidazopyridine PI3K Inhibitor with Anticancer Activity in Non-Small Cell Lung Cancer Cells. *Oncol. Rep.* **2013**, *30*, 863–869. https://doi.org/10.3892/or.2013.2499.
6. Theresa O'Malley; Alling, T.; Early, J.V.; Wescott, H.A.; Kumar, A.; Moraski, G.C.; Miller, M.J.; Masquelin, T.; Hipskind, P.A.; Parish, T. Imidazopyridine Compounds Inhibit Mycobacterial Growth by Depleting ATP Levels. *Antimicrob. Agents Chemother.* **2018**, *62*, e02439-17. https://doi.org/10.1128/AAC.02439-17.
7. Saif, M.Z.; Esha, N.J.I.; Quayum, S.T.; Rahman, S.; Al-Gawati, M.A.; Alsowygh, G.; Albrithen, H.; Alodhayb, A.N.; Poirier, R.A.; Uddin, K.M. Investigating the Potential of 6-Substituted 3-Formyl Chromone Derivatives as Anti-Diabetic Agents Using in Silico Methods. *Sci. Rep.* **2024**, *14*, 13221. https://doi.org/10.1038/s41598-024-63237-y.
8. Rentería-Gómez, A.; Islas-Jácome, A.; Cruz-Jiménez, A.E.; Manzano-Velázquez, J.C.; Rojas-Lima, S.; Jiménez-Halla, J.O.C.; Gámez-Montaño, R. Synthesis of 2-Tetrazolylmethyl-Isoindolin-1-Ones via a One-Pot Ugi-Azide/(N-Acylation/ *Exo* -Diels–Alder)/Dehydration Process. *ACS Omega* **2016**, *1*, 943–951. https://doi.org/10.1021/acsomega.6b00281.
9. Alvarez-Rodríguez, N.V.; Islas-Jácome, A.; Rentería-Gómez, A.; Cárdenas-Galindo, L.E.; Unnamatla, M.V.B.; Gámez-Montaño, R. Synthesis of 1′-Tetrazolylmethyl-Spiro[Pyrrolidine-3,3′-Oxindoles] via Two Coupled One-Pot Processes Ugi-Azide/Pictet–Spengler and Oxidative Spiro-Rearrangement. *New J. Chem.* **2018**, *42*, 1600–1603. https://doi.org/10.1039/C7NJ03829A.
10. Rentería-Gómez, A.; Islas-Jácome, A.; Jiménez-Halla, J.O.C.; Gámez-Montaño, R. Regiospecific Synthesis of 1-Acetamide-5-Methoxy-2-Oxindoles in Two Steps: (Ugi-SN2)/Xanthate Mediated Free Radical Cyclization. *Tetrahedron Lett.* **2014**, *55*, 6567–6570. https://doi.org/10.1016/j.tetlet.2014.10.026.
11. Cano, P.A.; Islas-Jácome, A.; González-Marrero, J.; Yépez-Mulia, L.; Calzada, F.; Gámez-Montaño, R. Synthesis of 3-Tetrazolylmethyl-4H-Chromen-4-Ones via Ugi-Azide and Biological Evaluation against Entamoeba Histolytica, Giardia Lamblia and Trichomona Vaginalis. *Bioorganic Med. Chem.* **2014**, *22*, 1370–1376. https://doi.org/10.1016/j.bmc.2013.12.069.
12. Rentería-Gómez, M.A.; Islas-Jácome, A.; Pharande, S.G.; Vosburg, D.A.; Gámez-Montaño, R. Synthesis of Tris-Heterocycles via a Cascade IMCR/Aza Diels-Alder + CuAAC Strategy. *Front. Chem.* **2019**, *7*, 546.
13. Pharande, S.G.; Rentería-Gómez, M.A.; Gámez-Montaño, R. Synthesis of Polyheterocyclic Dimers Containing Restricted and Constrained Peptidomimetics via IMCR-Based Domino/Double CuAAC Click Strategy. *Molecules* **2020**, *25*, 5246.

14. Kaveti, B.; Ramírez-López, S.C.; Gámez Montaño, R. Ultrasound-Assisted Green One-Pot Synthesis of Linked Bis-Heterocycle Peptidomimetics via IMCR/Post-Transformation/Tandem Strategy. *Tetrahedron Lett.* **2018**, *59*, 4355–4358. https://doi.org/10.1016/j.tetlet.2018.10.062.
15. Claudio-Catalán, M.Á.; Pharande, S.G.; Quezada-Soto, A.; Kishore, K.G.; Rentería-Gómez, A.; Padilla-Vaca, F.; Gámez-Montaño, R. Solvent- and Catalyst-Free One-Pot Green Bound-Type Fused Bis-Heterocycles Synthesis via Groebke–Blackburn–Bienaymé Reaction/SNAr/Ring-Chain Azido-Tautomerization Strategy. *ACS Omega* **2018**, *3*, 5177–5186. https://doi.org/10.1021/acsomega.8b00170.
16. Unnamatla, M.V.B.; Islas-Jácome, A.; Quezada-Soto, A.; Ramírez-López, S.C.; Flores-Álamo, M.; Gámez-Montaño, R. Multicomponent One-Pot Synthesis of 3-Tetrazolyl and 3-Imidazo[1,2-a]Pyridin Tetrazolo[1,5-a]Quinolines. *J. Org. Chem.* **2016**, *81*, 10576–10583. https://doi.org/10.1021/acs.joc.6b01576.
17. Kishore, K.G.; Basavanag, U.M.V.; Islas-Jácome, A.; Gámez-Montaño, R. Synthesis of Imidazo[1,2-a]Pyridin-Chromones by a MW Assisted Groebke–Blackburn–Bienaymé Process. *Tetrahedron Lett.* **2015**, *56*, 155–158. https://doi.org/10.1016/j.tetlet.2014.11.047.
18. Shaabani, A.; Hooshmand, S.E. Choline Chloride/Urea as a Deep Eutectic Solvent/Organocatalyst Promoted Three-Component Synthesis of 3-Aminoimidazo-Fused Heterocycles via Groebke–Blackburn–Bienayme Process. *Tetrahedron Lett.* **2016**, *57*, 310–313. https://doi.org/10.1016/j.tetlet.2015.12.014.