ISOCYANIDE-BASED MULTICOMPONENT REACTIONS

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ISOCYANIDE-BASED MULTICOMPONENT REACTIONS

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EDITORIAL
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Editorial: Isocyanide-Based Multicomponent Reactions

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Editorial on the Research Topic

Isocyanide-Based Multicomponent Reactions

Multicomponent reactions are an inspiring class of transformations in organic chemistry (Zarganes-Tzitzikas et al., 2015). These reactions, which incorporate three or more reactants into a single reaction product, offer advantages over traditional bimolecular reactions. Multicomponent reactions accelerate exploration of chemical space by reducing the number of synthetic and purification operations required to make a given target. The accompanying atom economy of multicomponent reactions further improve the sustainability of the chemical enterprise. The mechanisms of multicomponent reactions also challenge our understanding of subtle reactivity principles. Besides green chemistry attributes and mechanistic beauty, a key feature of multicomponent reactions that has not yet been fully embraced is the easy engineering of functional materials (Afshari and Shaabani, 2018). Functions can range from affinity ligands for immunoglobulin purification (Kruljec and Bratkovič, 2017) to imaging compounds in biological systems (Lin et al., 2017) to proteome-wide mapping of protein-protein interactions (Kambe et al., 2014) to molecular machines (García-González et al., 2018) to molecular keys for applications in advanced encryption standard cryptography with molecular steganography (Boukis et al., 2018). According to the basic principle *form follows function*, forms can be assembled in a unique fashion via multicomponent reactions from building blocks connected to certain properties. Such properties can be chirality, ligands for metals, fluorescence, extended π-systems with tunable HOMO–LUMO distances, or hydrogen bond donor-acceptor configurations. An emerging and rapidly growing field in this respect is the use of multicomponent reactions in polymer science and engineering (Llevot et al., 2017).

Among the most well-known and diverse class of multicomponent reactions are those in which an isocyanide (a.k.a., isonitrile) reagent is incorporated in the product. Isocyanide-based multicomponent reactions were some of the very first multicomponent reactions discovered in organic chemistry. Mario Passerini reported the reaction of an aryl isocyanide with ketones and carboxylic acids, the first isocyanide-based three-component reaction, nearly a century ago (Passerini, 1921). Ivar Ugi disclosed the first isocyanide-based four component reaction almost 40 years later (Ugi and Steinbrückner, 1960). Ugi's insights about the mechanisms of these multicomponent reactions have stimulated discoveries of numerous reaction variants. Ugi also recognized the potential for multicomponent reactions to enable combinatorial library synthesis and to serve as platforms for diversity-oriented synthesis. These pillars have sustained more than a half century of research into isocyanide-based multicomponent reactions. As we reflect upon the state-of-the-art in the field, these themes remain pervasive as synthetic organic chemists apply

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isocyanide-based multicomponent reactions to address challenges in biology (Neochoritis et al., 2019), polymers (Kakuchi, 2019), and materials science (Afshari and Shaabani, 2018).

Through continued method development and synergies with emerging technologies, the scope of isocyanide-based multicomponent reactions continues to expand. Several contributions to this themed collection highlight ongoing efforts to mine the richness and complexity of these reactions. Golantsov et al. report a novel reaction in which aryl(indol-3-yl)methylium tetrafluoroborates, aromatic isocyanides, and alcohols yield alky aryl(indol-3-yl)acetimidates. The indolium salts are derived from the condensation of *N*-alkyl indoles and aromatic aldehydes, which makes this a four-component reaction. Salvador and Andrade demonstrate dramatic improvements in efficiency and scalability of the Passerini three-component reaction involving arylglyoxals through adoption of the microwave-to-flow paradigm. Employing 1-unsubstituted 2-aminoimidazoles in the Groebke–Blackburn–Bienaymé reaction (Bienaymé and Bouzid, 1998; Blackburn, 1998; Groebke et al., 1998), Driowya et al. describe a novel method in which 1*H*-imidazo[1,2-*a*]imidazole-5-amines are prepared. Products of isocyanide-based multicomponent reactions, such as the classic Ugi reaction, are also versatile starting points for further diversification. Zidan et al. apply their recently developed "dianionic amide strategy" toward alkylation of Ugi reaction products.

Isocyanide-based multicomponent reactions have been highly successful in rapidly enumerating members of compound libraries, especially in drug discovery. Structural diversity in these libraries is critical to the elucidation of structure-activity relationships that drive development of new products and technologies. The emergence of resistance to drugs demands a deep cabinet of safe and effective drugs, in addition to a pipeline of new drug candidates. Derivatization of existing drugs represents one approach to generating libraries of compounds with high potential for translation to the clinic. Pedrola et al. exemplify this approach by derivatizing the antibiotic trimethoprim, an α-aminoazine, via the Groebke–Blackburn–Bienaymé reaction. Impressively, the resulting focused library contains compounds that are effective against methicillin-resistant *Staphylococcus aureus* (MRSA). Ochs et al. comprehensively investigate photoinduced electron transfer in a library of unimolecular exciplexes synthesized via the Ugi reaction.

Access to unexplored regions of chemical space is a pressing challenge for synthetic chemistry. Campaigns to discover biologically active compounds have saturated regions of chemical space identified from natural products and available in libraries of drug-like compounds. Judicious selection or design of the reactants in a given multicomponent reaction can afford previously unknown classes of compounds as products. Shaabani et al. provide such an example in their synthesis of oxazepine-quinazolone bis-heterocyclic scaffolds via an Ugi four-center three-component reaction. Yasaei et al. describe their discovery of an isocyanide-based multicomponent reaction that yields 5-(tosylquinolin-3-yl)oxazoles.

In conclusion, the past century has witnessed maturation of isocyanide-based multicomponent reactions from their seminal discovery to their present expansion into fields that rely upon chemical tools. Hallmarks of these reactions, such as sustainability and versatility, should motivate continued exploration of these powerful reactions as well as their adoption by researchers working beyond chemical synthesis. We hope that this themed collection helps to inspire readers embrace these opportunities in the century ahead.

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All authors listed have made a substantial, direct and intellectual contribution to the work, and approved it for publication.

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ORIGINAL RESEARCH
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Raising the Diversity of Ugi Reactions Through Selective Alkylations and Allylations of Ugi Adducts

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We report here selective Tsuji-Trost type allylation of Ugi adducts using a strategy based on the enhanced nucleophilicity of amide dianions. Ugi adducts derived from aromatic aldehydes were easily allylated at their peptidyl position with allyl acetate in the presence of palladium catalysts. These substitutions were compared to more classical transition metal free allylations using allyl bromides.

Keywords: Ugi reaction, allylation, palladium, Tsuji-Trost reaction, metathesis, piperidines

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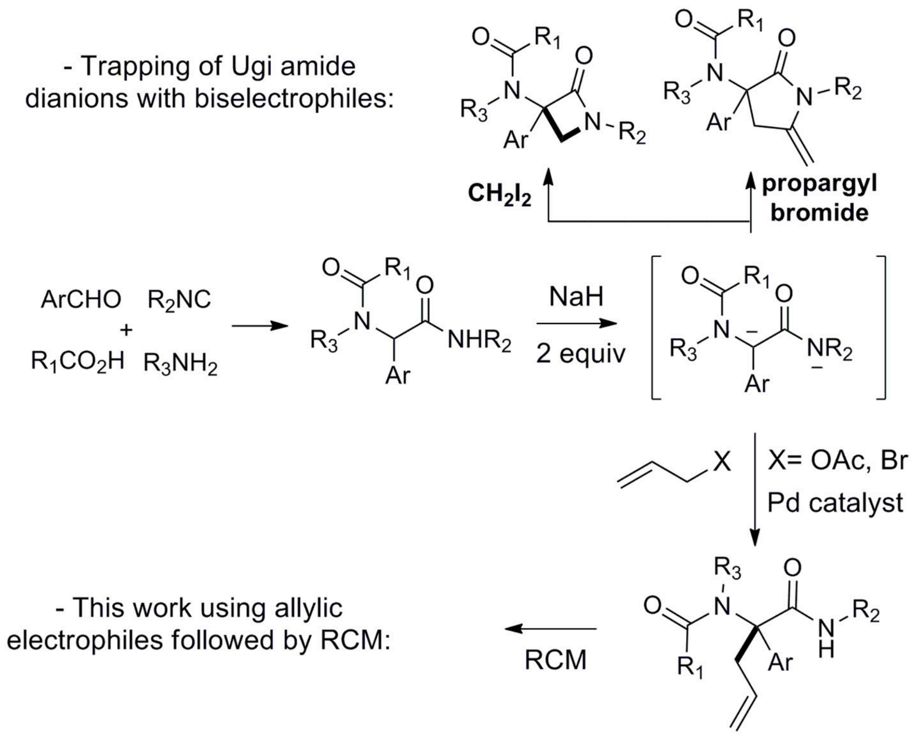
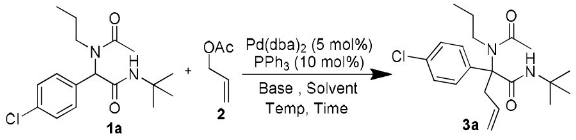
INTRODUCTION

Since its discovery and even more after the 1980's, the Ugi reaction has fascinated chemists with the high diversity brought by its four components nature together with its impressive functional tolerance (Dömling and Ugi, 2000; Hulme and Gore, 2003; Orru and De Greef, 2003; Zhu and Bienaymé, 2005; Dömling, 2006; Dömling et al., 2012; Zhu et al., 2014; Boyarskiy et al., 2015; Váradi et al., 2016; Lei et al., 2018). Besides important efforts devoted to the preparation of libraries of heterocycles through cyclization of properly functionalized Ugi adducts (Tempest, 2005; Sunderhaus and Martin, 2009; Ivachtchenko et al., 2010; Orru and Ruijter, 2010a,b; Sadjadi and Heravi, 2011; Eckert, 2012; Sharma et al., 2015), a number of studies have focused on raising the diversity by letting Ugi adducts react in further intermolecular couplings (Elders et al., 2009; Brauch et al., 2010; Zarganes-Tzitzikas et al., 2015a,b; Kaur et al., 2016). In contrast with the previous intramolecular couplings, these strategies (such as the combination of MCRs) are much more sensitive to steric hindrance and require more attention in selecting the functionalities required for further couplings. For this reason, most transformations involving the peptidyl position of Ugi adducts are limited to intramolecular reactions (Bossio et al., 1997; Trifilenkov et al., 2007; Salcedo et al., 2008; El Kaïm et al., 2011; Tyagi et al., 2013; Zhang et al., 2013; Ben Abdessalem et al., 2015; Ghandi et al., 2015; Vachhani et al., 2015; Li et al., 2016). We recently proposed a dianionic amide strategy to raise the nucleophilic behavior of Ugi adducts derived from aromatic aldehydes and demonstrated the interest of this approach using bis-electrophilic derivatives prone to trap the dianions and form heterocycles (**Scheme 1**) (Zidan et al., 2017, 2018). Following the high yielding cyclizations observed in these studies, we decided to explore more thoroughly the synthetic potential of these dianions (Thompson, 1994; Langer and Freiberg, 2004) toward more simple electrophiles. We now wish to report further applications of this chemistry in Tsuji-Trost reactions as well as metal-free alkylations with bromide derivatives (**Scheme 1**).



SCHEME 1 | Reaction of Ugi amide dianion with mono and biselectrophiles.

TABLE 1 | Screening of various conditions[a].

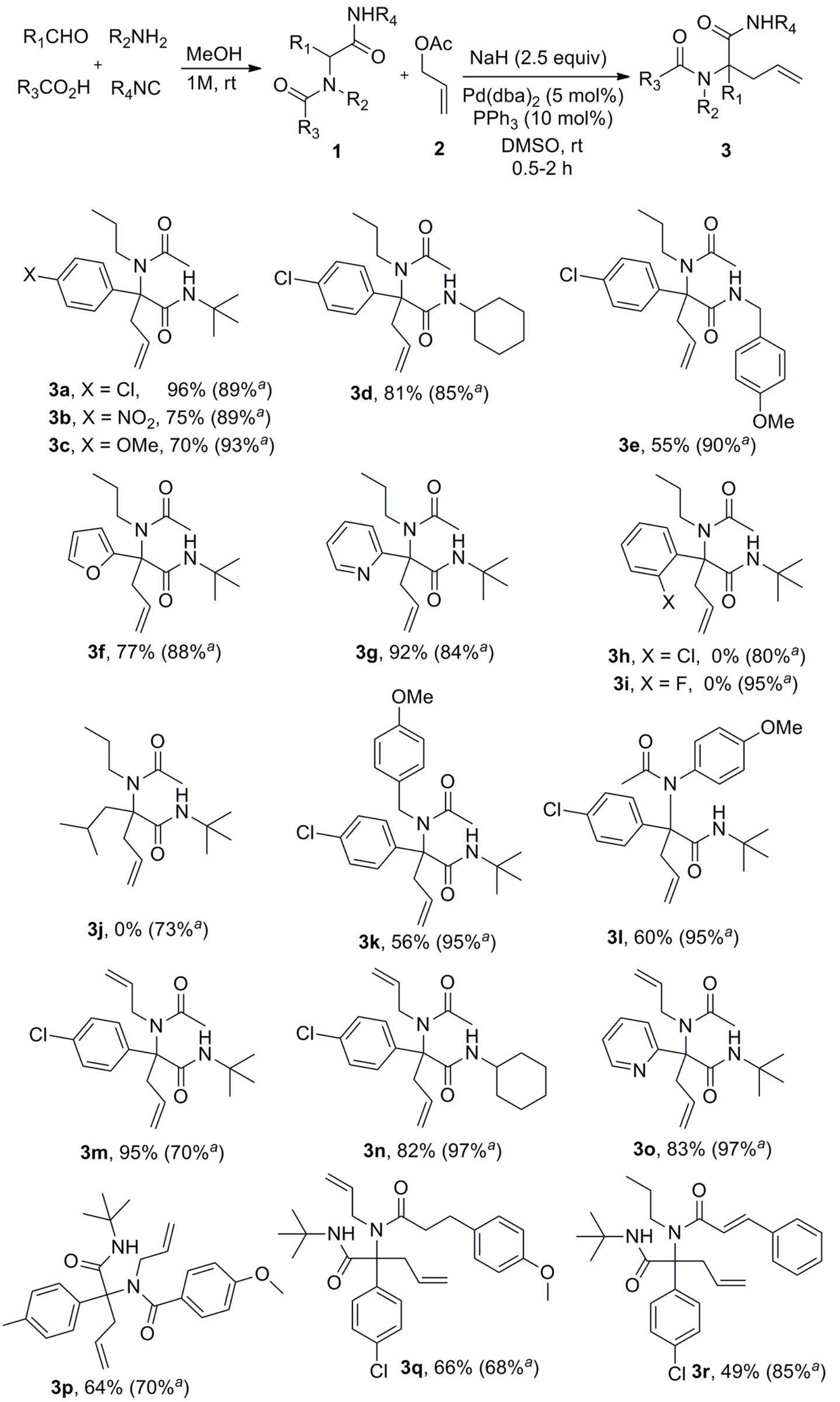


Entry	Base (equiv)	Solvent	Temp (°C)	Time (h)	Yield (%)
1	*t*-BuOK(2.5)	THF	reflux	2	65
2	*t*-BuOK(2.5)	DMF	70	12	70
3	KHMDS (2.5)	THF	reflux	1	95
4	KHMDS (2.5)	THF	50	1	93
5	KHMDS (1.3)	THF	50	1	37
6	KHMDS (2.5)	THF	rt	1	88
7	NaH (2.5)	THF	reflux	12	45
8	NaH (2.5)	DMF	70	12	50
9	**NaH (2.5)**	**DMSO**	**rt**	**1**	**96**
10[b]	NaH (2.5)	DMSO	rt	12	Traces
11[c]	NaH (2.5)	DMSO	rt	12	80
12[d]	NaH (2.5)	DMSO	rt	1	94
13[e]	KHMDS (2.5)	THF	rt	12	-

[a] *Reaction conditions:* ***1a*** *(0.5 mmol),* **2** *(0.75 mmol), Pd(dba)$_2$ (0.025 mmol), and PPh$_3$ (0.05 mmol) in solvent (0.5 M).* [b] *Using Xantphos (5 mol%) instead of PPh$_3$.* [c] *Using Johnphos (10 mol%) instead of PPh$_3$.* [d] *Using Pd(PPh$_3$)$_4$ (5 mol%) instead of Pd(dba)$_2$/PPh$_3$.* [e] *Reaction without Pd(dba)$_2$ and PPh$_3$. Bold font indicates the selected value for the optimization.*

RESULTS AND DISCUSSION

Following our interest in Tsuji-Trost reactions involving isocyanide based MCRs (Dos Santos and El Kaïm, 2014; Cordier et al., 2015; El Mamouni et al., 2016), we decided to explore the behavior of Ugi adducts dianions toward allyl acetate. Besides the efficiency and regioselectivity issues of the reaction of these dianions with π-allyl palladium complexes, such study might bring interesting pathways for further enantioselective



3a, X = Cl, 96% (89%[a])
3b, X = NO_2, 75% (89%[a])
3c, X = OMe, 70% (93%[a])

3d, 81% (85%[a])

3e, 55% (90%[a])

3f, 77% (88%[a])

3g, 92% (84%[a])

3h, X = Cl, 0% (80%[a])
3i, X = F, 0% (95%[a])

3j, 0% (73%[a])

3k, 56% (95%[a])

3l, 60% (95%[a])

3m, 95% (70%[a])

3n, 82% (97%[a])

3o, 83% (97%[a])

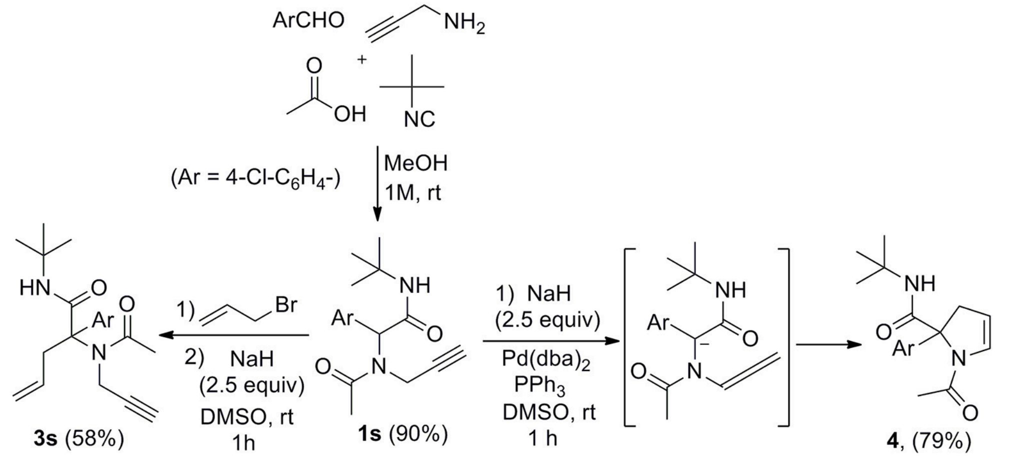
3p, 64% (70%[a])

3q, 66% (68%[a])

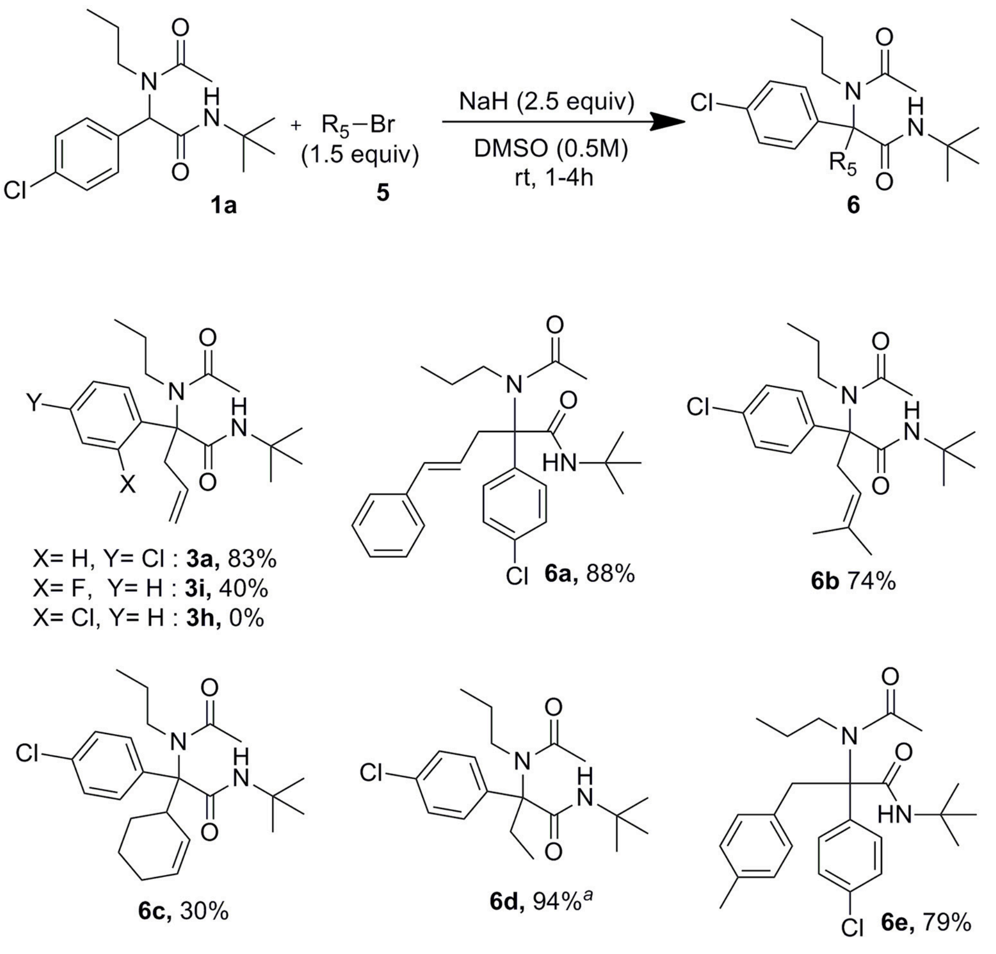
3r, 49% (85%[a])

[a]Isolated yields of Ugi adducts.

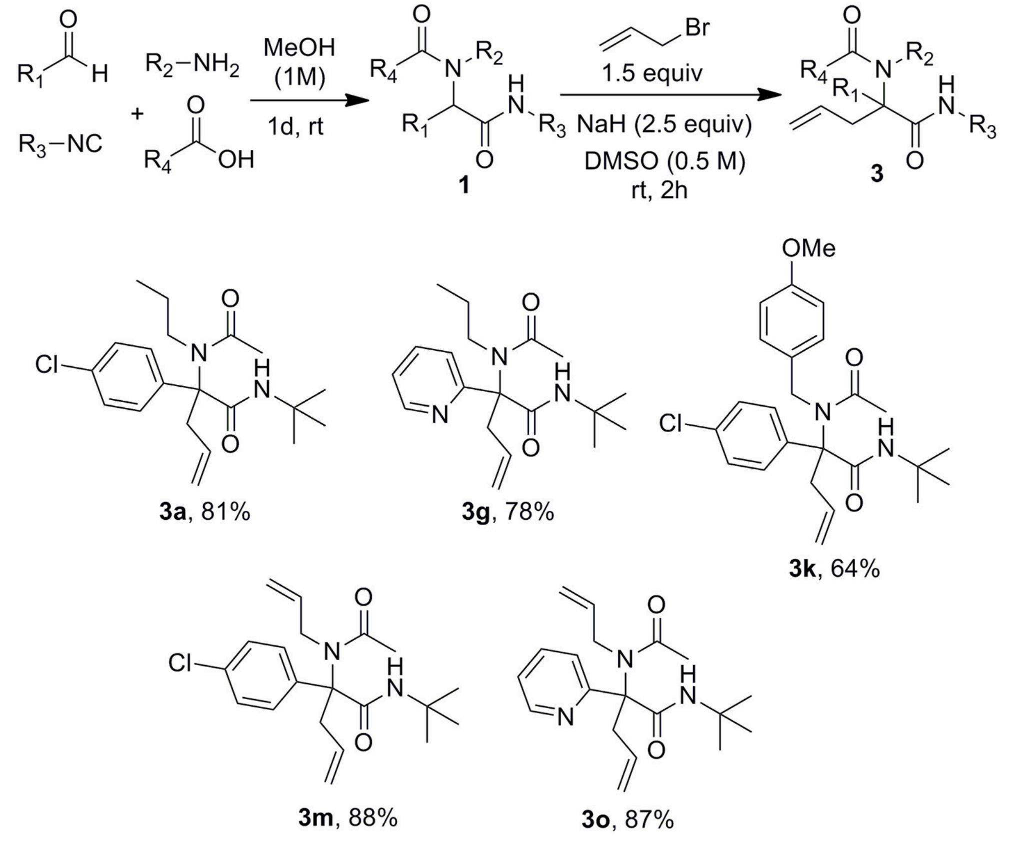
SCHEME 2 | Scope of the Ugi/Tsuji-Trost cascade.



SCHEME 3 | Allylation of Ugi propargyl adduct.



SCHEME 4 | Scope of alkylating agents.

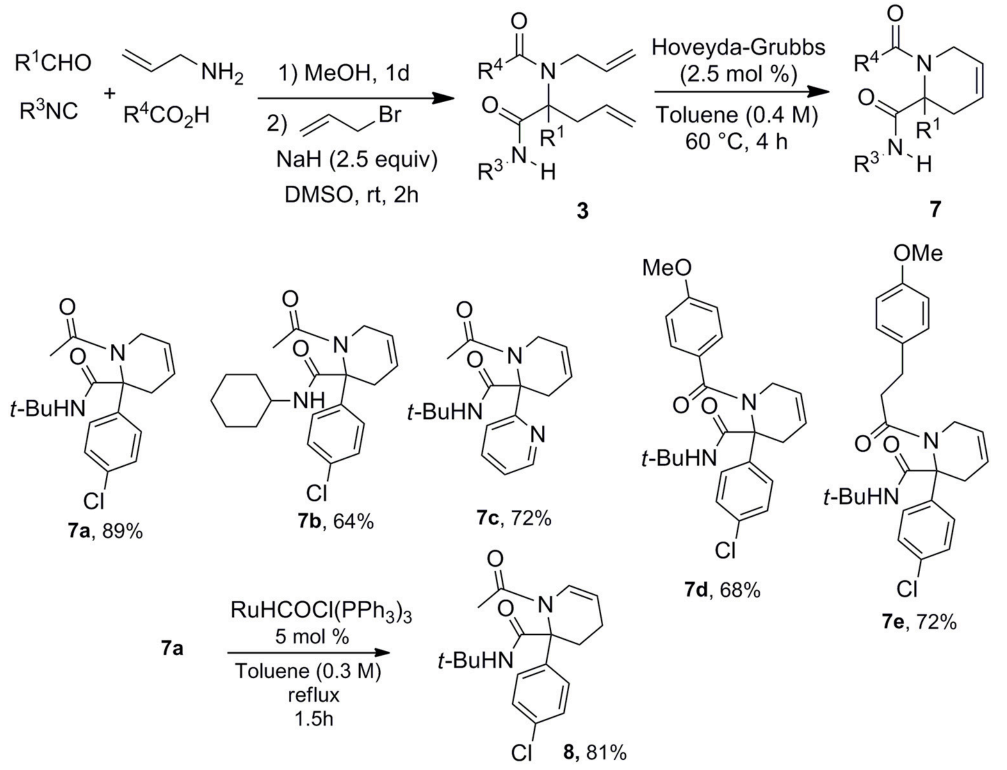


SCHEME 5 | Cascade one pot reaction.

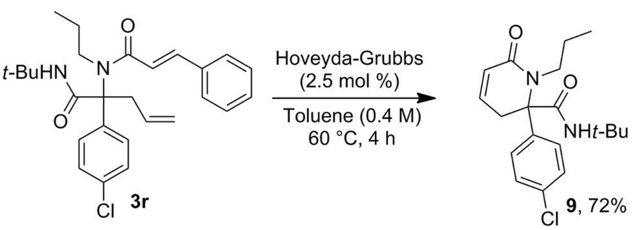
approaches. For this study, Ugi adduct **1a** was selected due to its good behavior in our previous studies with propargyl bromide and diiodomethane. It was prepared in 89% yield from 4-chloro-benzaldehyde, propylamine, acetic acid and *tert*-butylisocyanide (**Table 1**). When **1a** was heated with allyl acetate in THF using 2.5 equivalents of potassium *tert*-butoxide together with a Pd(dba)$_2$/PPh$_3$ catalytical couple, we were delighted to observe a selective C-allylation of **1a** giving **3a** in 65% isolated yield after 2 h refluxing (entry 1, **Table 1**).

Different bases in various solvents were then evaluated using the same palladium/phosphine couple. The enhanced nucleophilicty of the 1,3-amide dianion toward the π-allyl palladium cationic complex was confirmed experimentally by comparing the use of 2.5 and 1.3 equiv of KHMDS (affording respectively 93 and 37% isolated yields: entries 4 and 5, **Table 1**). NaH in DMSO, gave the best conditions affording to our delight a nearly quantitative yield of **3a** in only 1 h at room temperature (entry 9, **Table 1**). Further modifications of the catalyst using more complex phosphines led to longer reaction time and lower yields (entries 10–12, **Table 1**), while in absence of palladium source, no product was observed (entry 13, **Table 1**).

A set of Ugi adducts were then prepared in methanol and submitted to these optimized allylation conditions. The results are gathered in **Scheme 2**. As observed in our previous studies (Zidan et al., 2017, 2018), an aryl group tethering the peptidyl position is required for efficient allylation. Indeed, Ugi adduct **1j** prepared from isovaleraldehyde failed to form the expected **3j** probably due to the inability to form the dianionic intermediate with this less acidic substrate. Surprisingly, we didn't observe much correlation between yields and the electronic nature of the aldehyde as shown by the similar yields obtained with both 4-nitro or 4-methoxy substituted derivatives **3b** and **3c**. A much stronger effect of the substitution partner of the aromatic moiety was observed with 2-chloro substituted Ugi adduct **1h** which failed to give any adduct under these conditions as observed with **1j**. The same behavior was observed for the attempted synthesis of the fluoro analog **3i**. This lack of reactivity can probably be explained by the steric hindrance brought by substituents at the ortho position preventing to reach the planar geometry required for benzylic anion stabilization. Initial trials on enantioselective allylations were rather deceiving. When triphenylphosphine was replaced by BINAP (5mol %) for the reaction of **1a** with **2a**, **3a** could be formed rapidly in good yield (89%) but poor enantioselectivity (5%) whereas the use of Trost ligand (DACH-phenyl) failed to give any allylation reaction. A wider scope of chiral ligands as well as alternative solvents allowing lower temperatures will have to



SCHEME 6 | Ugi/allylation/RCM strategy.



SCHEME 7 | Ugi/allylation/MCR toward piperidones.

be evaluated to reach an enantioselective version. The reaction could not be extended to more substituted allylic acetate derivatives such as cinnamyl acetate. The latter failed to react with Ugi adduct **1a** even under prolonged heating, leading only to saponification of the ester and isolation of cinnamyl alcohol.

Submitting propargylamine-derived Ugi adduct **1s** to the same reaction conditions didn't afford any allylated product but resulted in the clean formation of 2,3-dihydropyrrole **4** (**Scheme 3**), a reaction already reported by Miranda et al. (Polindara-García and Miranda, 2012). They could isolate the same dihydropyrrole **4** in 36% yield treating **1s** with *t*-BuOK (2.5 equiv) in THF, while we could obtain 79% yield with our conditions. This selectivity was not very surprising when considering the respective intra and intermolecular properties of the two pathways. However, the ability to form enyne derivatives from Ugi adducts together with the interest of reversing a preferred selectivity were challenging enough to explore different set of conditions. Indeed, the dihydropyrrole formation probably involves a first isomerization into allene followed by further 5-endo-trig cyclization. This could leave some space for a previous intermolecular allylation if the lifetime of the dianion could be reduced by increasing the kinetic of the allylation step. Introducing the allyl acetate together with the palladium catalyst and the Ugi adduct in DMSO followed by the addition of the base resulted in a lower 54% yield of **4** together with a complex mixture of allylated products. We next explored the use of allyl bromide as a potential electrophilic species in the absence of palladium. When adding the latter to Ugi adduct **1s** followed by NaH, we were delighted to observe the expected enyne **3s** obtained in 58% isolated yield without any trace of dihydropyrrole (**Scheme 3**). This interesting control of the selectivity offers an attractive access to enyne derivatives for further cyclization studies.

These conditions settled with allyl bromide proved useful as well for the reaction of other alkyl bromides and iodides as shown in **Scheme 4**. The lowest 30% yield of **6c** obtained using 3-bromocyclohex-1-ene may be explained by the use of secondary halides together with the high steric hindrance around the peptidyl position of the Ugi adduct. In order to confirm further the importance of forming dianionic intermediates, the formation of **3a** was attempted using allyl bromide in excess (1.5 equiv) but reducing the amount of sodium hydride to 0.9 equiv. In this case, only traces of allylated compound could be identified after 2 h at rt whereas the reaction was completed after the same time when using 2.5 equiv of sodium hydride. Interestingly, whereas under Tsuji-Trost type conditions we couldn't observe any allylation of both 2-chloro and 2-fluoro substituted derivatives **1h** and **1i**, the latter gave us a moderate 40% isolated yields of **3i** when using just sodium hydride with allyl bromide.

A further interest of the use of palladium free conditions may be found in the ability to carry the reaction starting directly from the four Ugi components. Indeed remaining isocyanides after the Ugi reaction are potentially inhibitor for most classical palladium catalyzed processes making thus one-pot processes difficult to achieve (El Kaim et al., 2008)[1]. After completion of the Ugi adduct, the methanol was evaporated under reduced pressure. The solvent was then replaced by DMSO. Addition of sodium hydride followed by allyl bromide afforded the final allylated Ugi adducts in good overall yields (**Scheme 5**).

With this easy allylation of Ugi adducts in hand, we decided to take advantage of the diversity offered by the latter coupling to explore Ugi/allylation/Ring Closure Methathesis (RCM) strategies toward various nitrogen based heterocycles. The use of RCM as Ugi post-condensation has already demonstrated its power for the formation of 5, 6-membered heterocycles as well as macrocyclic derivatives (Banfi et al., 2003; Beck et al., 2003; Hebach and Kazmaier, 2003; Ribelin et al., 2007; Ku et al., 2011). However, the synthetic potential of these strategies is in a way limited by the need of introducing the two allylated moieties at an early stage which reduces the diversity offered by the two-step process. The late stage allylation we propose is highly versatile allowing to settle the strategy with a single alkenyl moiety in the starting components. Thus using allyl amine, we could easily prepare a library of piperidines with five points of diversity (**Scheme 6**).

This access to 3,4-dehydropiperidine derivatives **7** could be further enriched by a potential isomerization into cyclic enamines as demonstrated by the ruthenium hydride catalyzed conversion of **7a** into **8** (**Scheme 6**). The versatility of the method can be pictured by the alternative choice of the alkenyl moiety on the acidic component such as in cinnamic acid offering now a very simple access to 3,4-dehydropiperidine-2-one **9** (**Scheme 7**).

CONCLUSION

In summary, we have extended the potential of the Ugi reaction using 1,3-amide dianionic species as intermediates for efficient allylations at the peptidyl moiety of Ugi adducts. The procedure raises the diversity of Ugi adducts and offers unique opportunities for the preparation of nitrogen based heterocycles through association with ring closure metathesis (**Supplementary Data Sheet 1**). The power of the latter strategy has been demonstrated by the preparation of various piperidines which are important scaffolds for medicinal applications.

AUTHOR CONTRIBUTIONS

AZ was responsible for designing and performing the experiments. AZ, AE-N, NA, AA, and LE discussed the evolution of the project and revised the manuscript together. LE and AA directed the project and wrote the publication.

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We dedicate this work to our colleague Mohamed Ali Hassan who passed away few months before the end of this study. We gratefully acknowledge a Scholarship from the Egyptian Government, which was awarded to AZ.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fchem.2019.00020/full#supplementary-material

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[1] However, one-pot processes may be envisioned if the remaining isocyanide is destroyed by an acidic hydrolysis prior palladium addition.

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Three-Component Reaction of 3-Arylidene-3*H*-Indolium Salts, Isocyanides, and Alcohols

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A novel isocyanide-based multicomponent synthesis of alkyl aryl(indol-3-yl)acetimidates has been established. Starting from aryl(indol-3-yl)methylium tetrafluoroborates, aromatic isocyanides and alcohols, the imidates were obtained in moderate to very good yields. Consecutive four-component synthesis of the above mentioned imidates from N-alkylindoles, aromatic aldehydes, aromatic isocyanides and alcohols was also proposed. In addition, it was shown that in the presence of water, aryl(indol-3-yl)methylium tetrafluoroborates reacted with isocyanides to furnish aryl(indol-3-yl)acetamides.

Keywords: multicomponent reactions, isocyanides, indoleninium ions, aryl(indol-3-yl)methylium ions, imidates

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INTRODUCTION

Multicomponent reactions (MCRs) serve as a powerful and widely used instrument in organic synthesis (Shiri, 2012; Müller, 2014; Zarganes-Tzitzikas et al., 2015; Zhu et al., 2015; Levi and Müller, 2016). A special place among them is occupied by transformations with the participation of isocyanides, unique reagents where nucleophiles and electrophiles attack the same atom (for a book on isocyanides, see Nenajdenko, 2012; for selected reviews on isocyanide-based MCR, see Dömling and Ugi, 2000; Dömling, 2006; Sadjadi et al., 2016). Common reaction partners in MCR with isocyanides are iminium salts, carbonyl compounds (or oxocarbenium ions), and electron-deficient alkynes (Ugi, 1962; Banfi and Riva, 2005; De Moliner et al., 2011). Several examples of interaction between isocyanides and activated alkenes were reported (Saegusa et al., 1972; Person et al., 1980; Shaabani et al., 2002; Maltsev et al., 2006; Mironov et al., 2006; Jing et al., 2010; Soleimani and Zainali, 2011; Soleimani et al., 2011, 2013). Reactions of isocyanides with α,β-unsaturated imines or the corresponding iminium salts with the possibility of 1,4-addition are still rare (Marchand et al., 1999; Fontaine et al., 2009; Shimizu et al., 2009). Particularly, such imine and iminium salts were used in a formal [4+1] cycloaddition reaction with the formation of a pyrrole ring (Marchand et al., 1999; Fontaine et al., 2009; Kaur et al., 2016). In our opinion, the interaction of isocyanides with α,β-unsaturated imines could well-evolve into a novel multicomponent reaction.

Considering that the indole scaffold is privileged from medicinal chemistry point of view (Barreiro, 2016), we decided to use 3-arylidene-3*H*-indolium salts as simple vinylogues of iminium ions. Alkylideneindoleninium (3-alkylidene-3*H*-indolium) ions (**I**) can be formed as intermediates by cleaving the leaving group from the α-position ("benzylic") of the substituent at the indole 3-position (**Figure 1A**) (For reviews, concerning generation and reactivity of alkylideneindolenine intermediates, see Enders et al., 2008; Shaikh et al., 2008; Palmieri et al., 2010; Wang et al., 2014; Zhuo et al., 2014; Jin et al., 2015; Palmieri and Petrini, 2016; Deb et al., 2017; Mei and Shi, 2017). Such intermediates are usually unstable and can react *in situ* with nucleophiles. This approach has

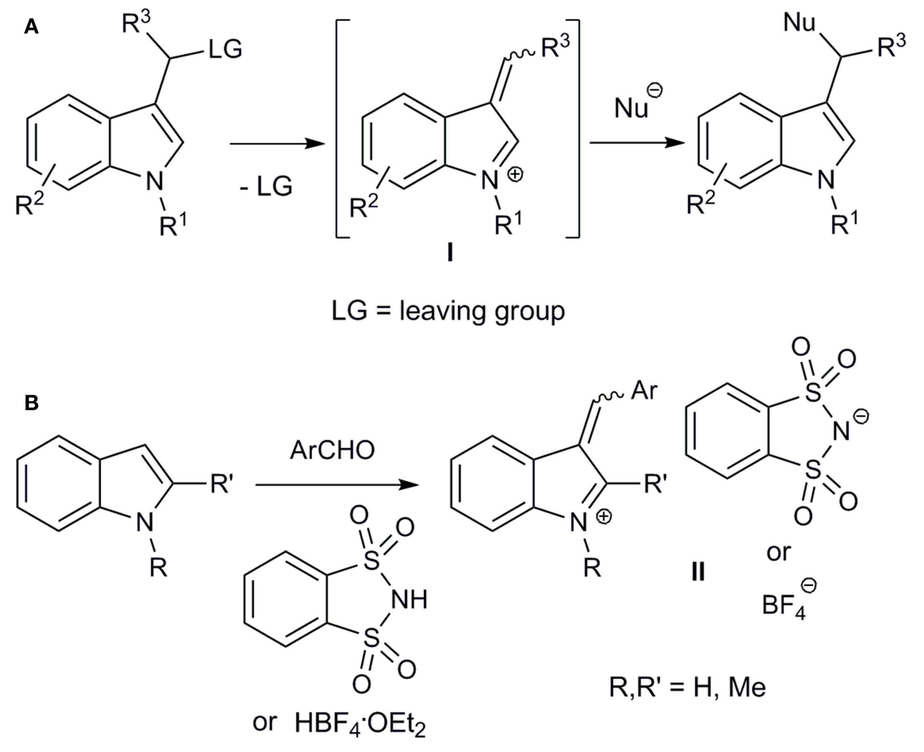

FIGURE 1 | *In situ* generation of alkylideneindoleninium intermediates **(A)** and synthesis of stable aryl(indol-3-yl)methylium salts **(B)**.

been widely used in the syntheses of various indole derivatives (Enders et al., 2008; Shaikh et al., 2008; Palmieri et al., 2010; Wang et al., 2014; Zhuo et al., 2014; Jin et al., 2015; Palmieri and Petrini, 2016; Deb et al., 2017; Mei and Shi, 2017).

Moreover, relatively stable 3-arylidene-3*H*-indolium (aryl(indol-3-yl)methylium) ions **II** were obtained by acid-catalyzed coupling of indoles and aryl aldehydes, and were isolated and characterized as *o*-benzenedisulfonimide salts (**Figure 1B**) (Barbero et al., 2012). The corresponding diarylmethanes were obtained by reduction of these salts (Barbero et al., 2012), and an organocatalytic addition of aliphatic aldehydes to such compounds was developed (Armenise et al., 2015). Recently, an efficient synthesis for a bench-stable aryl(indol-3-yl)methyl tetrafluoroborate has been proposed (**Figure 1B**) (Barbero et al., 2015; Follet et al., 2015). Lewis acidity of such obtained aryl(indol-3-yl)methylium ions and kinetics of their interaction with different nucleophiles, including allylsilanes, enol silyl ethers, triarylphosphines, pyridines, secondary amines, have been studied (Follet et al., 2015, 2016). It should also be mentioned that the vinylogous iminium character of salts **II** was confirmed by single-crystal X-ray diffraction analysis (Barbero et al., 2015; Follet et al., 2015).

To the best of our knowledge, reactions of alkylideneindolenines or the corresponding salts with isocyanides have not been published yet. Herein, we report the three-component reaction of 3-arylidenindolium salts with isocyanides and alcohols to form alkyl aryl(indol-3-yl)acetimidates.

RESULTS AND DISCUSSION

Starting salts **1a-f** were obtained by alkylation of the corresponding indoles followed by reaction of *N*-benzylindoles **2a-c** with aromatic aldehydes **3a-c** under conditions similar to a previously published procedure (**Figure 2**) (Follet et al., 2015). Tetrafluoroborates **1a-f** containing a benzyl group in the indole 1-position remained unchanged after being stored at room temperature for several weeks and turned out to be more stable than their methyl analogs, whose lability was observed previously (Follet et al., 2015). In solution salts **1a-f** exist as a mixture of *E*- and *Z*-isomers (for copies of NMR spectra of obtained compounds, see **Supplementary Material**), what was also noted for 2-unsubstituted derivatives earlier (Follet et al., 2015).

Next, the interaction of salt **1a** with *p*-methoxyphenyl isocyanide (**4a**) in methanol (**5a**) was performed at room temperature. After treating the reaction mixture with sodium bicarbonate solution, the imidate **6a** was isolated in moderate yield as a result of the expected three component interaction (**Figure 3**; **Table 1**, entry 1). This was stable upon chromatography on silica gel and further storage for several weeks. Unfortunately, our attempt to facilitate the reaction by heating was unsuccessful, due to significant tar formation (**Table 1**, entry 2). The addition of potassium carbonate as a base increased the yield (**Table 1**, entries 4, 7, 8), but led to the formation of ether **7**, resulting from the two-component reaction with methanol. Sodium or cesium carbonate had nearly the same effect, while Et_3N was less effective (**Table 1**, entries 3, 5, 6).

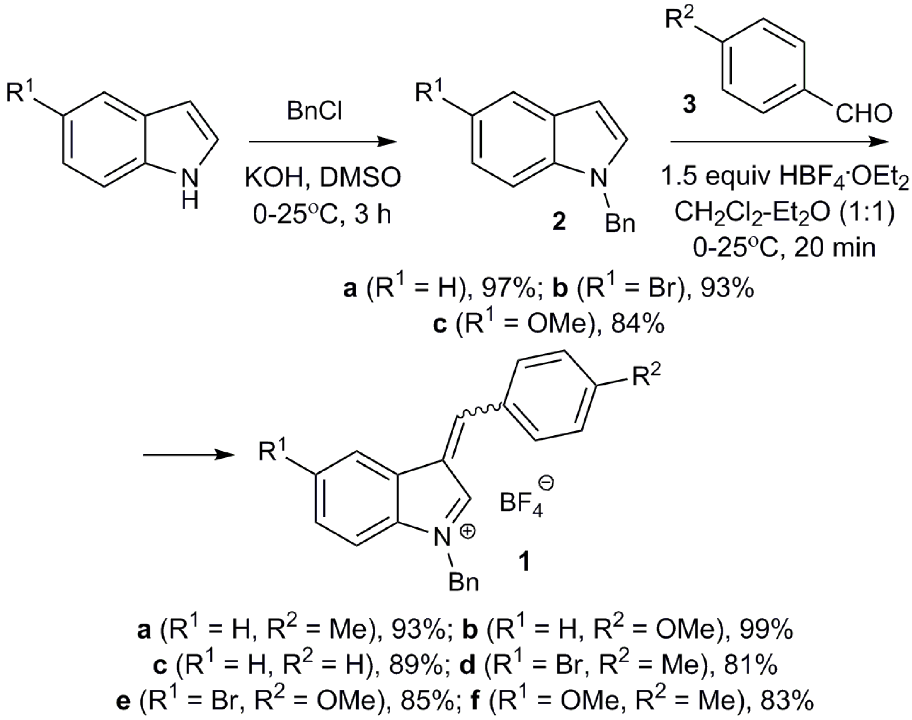

FIGURE 2 | Synthesis of 3-arylidene-*3H*-indolium salts **1**.

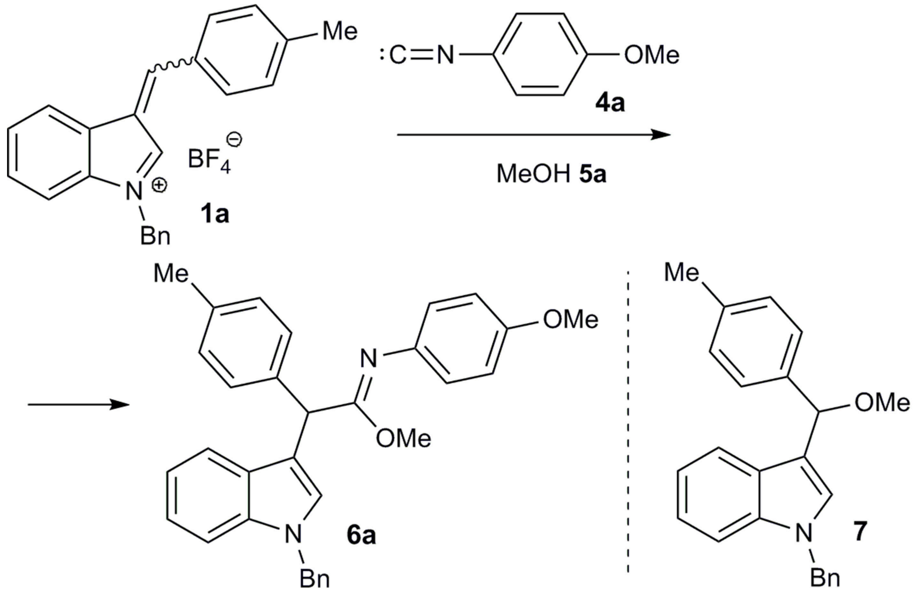

FIGURE 3 | Reaction optimisation for imidate **6a** synthesis.

The formation of methoxy derivative **7** was not observed when the reaction was carried out in acetonitrile with 4 equiv of methanol and 1.5 equiv. of K_2CO_3, (**Table 1**, entry 10). However, the highest yield of the target product **6a** was achieved by using a mixture of equal amounts of methanol and acetonitrile as solvent (**Table 1**, entry 12).

In these optimized conditions, the reaction was showing significant progress by TLC during the first 3 h. After 6 h, the yield did not change substantially (**Table 1**, entries 11 and 12). It is worth noting that increasing the amount of isocyanide resulted in a drop of the yield (**Table 1**, entry 9 vs. 7), whereas, performing the reaction without the addition

TABLE 1 | Reaction optimisation for imidate **6a** synthesis.

Entry	MeOH (equiv.)	Solvent	Base (equiv.)	Temperature (°C)	Time (h)	Yield (%)[d]
1[a]	80	MeOH	-	20	24 h	30
2[a]	80	MeOH	-	65	3 h	25
3[a]	80	MeOH	Na_2CO_3 (1.0)	20	12 h	45 (traces)
4[a]	80	MeOH	K_2CO_3 (1.0)	20	12 h	47 (traces)
5[a]	80	MeOH	Cs_2CO_3 (1.0)	20	12 h	43 (traces)
6[a]	80	MeOH	Et_3N (1.0)	20	12 h	36 (18)
7[a]	80	MeOH	K_2CO_3 (1.5)	20	12 h	51 (12)
8[a]	80	MeOH	K_2CO_3 (2.0)	20	12 h	48 (15)
9[b]	80	MeOH	K_2CO_3 (1.5)	20	12 h	28
10[a]	4	MeCN	K_2CO_3 (1.5)	20	12 h	48
11[a]	40	MeCN – MeOH (1:1)	K_2CO_3 (1.5)	20	6 h	63
12[a]	**40**	**MeCN – MeOH (1:1)**	**K_2CO_3 (1.5)**	**20**	**12 h**	**65**
13[c]	80	MeOH	K_2CO_3 (1.5)	20	12 h	(91)
14[c]	80	MeOH	-	20	24 h	(traces)

[a] *1.3 equiv.* ***4a.***

[b] *2.0 equiv.* ***4a.***

[c] *0 equiv.* ***4a.***

[d] *the yield of* ***7*** *is indicated in parentheses.*

of isocyanide in the presence of a base led to the formation of two-component reaction product **7**. Without the addition of base, this product was only formed in trace amounts (**Table 1**, entries 13, 14).

With the optimized conditions in hand, the interaction of salts **1a**-**f** with isocyanides **4a**-**d** and methanol was investigated (**Figure 4**; **Table 2**). Moreover, salts **1g**-**j** containing a methyl group at the indole nitrogen atom, which were obtained by a previously described procedure (Follet et al., 2015), were also involved. Reactions of aromatic isocyanides **4a**-**c** led to the corresponding imidates **6** in moderate to good yields. The best results were observed for salts derived from anisaldehyde (**Table 2**, entries 2, 5). Such results can be explained by stabilization of the 3-arylidene-3*H*-indolium salts **1b**,**h** with the donor substituent (MeO) and, consequently, by reducing the rate of the starting compound degradation under the reaction conditions, in comparison with more electrophilic salts **1a**,**c**,**g**,**i**. At the same time, the stronger electron-donating dimethylamino group notably reduced the electrophilicity of the substrate, which led to lowering the yield of the reaction product with isonitrile **4a** (**Table 2**, entry 7) (for electrophilicity parameters of salts **1j**-**g**, see Follet et al., 2015). Similarly, the presence of an electron-donating methoxy group at the indole 5-position slightly increased the yield of the corresponding imidate **6j** (**Table 2**, entry 1 vs. entry 10). The presence of a bromine atom in the same position decreased the yield (**Table 2**, entry 8, 9).

Among aromatic isocyanides, the best results were also achieved for isocyanide **4a** containing an electron-donating methoxy group. Furthermore, the alcohol component of this MCR could be varied and the reaction was carried out in a mixture of acetonitrile with alcohols **5b,c** (**Table 2**, entries 11-13).

It should be mentioned that, in case of the non-conjugated benzyl isocyanide **4d**, it was not possible to isolate the corresponding imidate **6s**. Within 12 h, the reaction did not show significant progress according to TLC. After work-up and purification by chromatography on silica gel, amide **8a** was isolated in a low yield along with compound **7** (**Table 2**, entry 19). Apparently, the amide **8a** was formed by hydrolysis of the corresponding imidate **6s**.

Next, the possibility of imidate synthesis from the indole and the aldehyde by a sequential one-pot four-component process, without isolation of the corresponding 3-arylidene-3*H*-indolium salt, was investigated (**Figure 5**; **Table 3**). After acid-catalyzed condensation of the aldehyde with 1-alkylindole, an excess of K_2CO_3 and a solution of isocyanide in the appropriate alcohol were added to the reaction mixture. To our great satisfaction, target imidate **6** was obtained in moderate to good yields.

Then we decided to extend our three-component imidate synthesis with the aim to obtain amides **8** (**Figure 6**; **Table 4**). As it turned out, addition of 10 volume % of water to the reaction mixture delivered the desired amides. Moreover, under these conditions, the reaction with benzyl isocyanide **4d** also proceeded very quickly. A white precipitate of the corresponding amide **8a** appeared almost immediately after isocyanide **4d** addition. The interaction with aromatic isocyanides **4a,c** was slightly slower but also efficient (**Table 4**, entries 7 and 8). Thus, 8 examples of amides **8** were obtained in a moderate to good yields employing this procedure (**Table 4**).

Previously, low yields were observed in formation of imidates with the conjugate addition of alkyl isocyanides to methyl acrylate and acrylonitrile in methanol (Saegusa et al., 1971). Amides were reported to be formed in reaction of dicyanoethylenes with isocyanides (Soleimani et al., 2011). Based on these facts and on the reported reactivity of 3-arylidene-3*H*-indolium salts (Follet et al., 2015, 2016), as well as on our own experiments, we suggest the following pathway for the multicomponent transformation of 3-arylidene-3*H*-indolium salts (**Figure 7**). The conjugate nucleophilic addition of isocyanide to the vinylogous iminium ion **1** leads to nitrilium salt **A**, which is further attacked by the nucleophile. This could be an alcoholate ion (or the corresponding alcohol). As a result, the imidate **4** is formed. Therefore, the role of the base in this process is to generate a small concentration of alcoholate ion as a strong nucleophile and to bind the released HBF_4.

The unsuccessful attempt of the three-component reaction with non-conjugated isocyanide **4d** can be explained by the

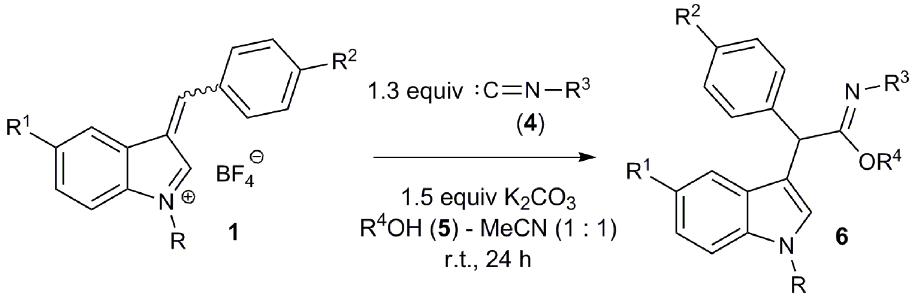

FIGURE 4 | Synthesis of imidates **6**.

TABLE 2 | Synthesis of imidates **6**.

Entry	Salt	R	R^1	R^2	Isocyanide	R^3	Alcohol	R^4	Product	Yield, %
1	**1a**	Bn	H	Me	**4a**	4-$MeOC_6H_4$	**5a**	Me	**6a**	65
2	**1b**	Bn	H	MeO	**4a**	4-$MeOC_6H_4$	**5a**	Me	**6b**	84
3	**1c**	Bn	H	H	**4a**	4-$MeOC_6H_4$	**5a**	Me	**6c**	56
4	**1g**	Me	H	Me	**4a**	4-$MeOC_6H_4$	**5a**	Me	**6d**	51
5	**1h**	Me	H	MeO	**4a**	4-$MeOC_6H_4$	**5a**	Me	**6e**	87
6	**1i**	Me	H	H	**4a**	4-$MeOC_6H_4$	**5a**	Me	**6f**	78
7	**1j**	Me	H	Me_2N	**4a**	4-$MeOC_6H_4$	**5a**	Me	**6g**	51
8	**1d**	Bn	Br	Me	**4a**	4-$MeOC_6H_4$	**5a**	Me	**6h**	47
9	**1e**	Bn	Br	MeO	**4a**	4-$MeOC_6H_4$	**5a**	Me	**6i**	52
10	**1f**	Bn	MeO	Me	**4a**	4-$MeOC_6H_4$	**5a**	Me	**6j**	71
11	**1a**	Bn	H	Me	**4a**	4-$MeOC_6H_4$	**5b**	Et	**6k**	53
12	**1b**	Bn	H	MeO	**4a**	4-$MeOC_6H_4$	**5b**	Et	**6l**	47
13	**1b**	Bn	H	MeO	**4a**	4-$MeOC_6H_4$	**5c**	*i*-Pr	**6m**	56
14	**1a**	Bn	H	Me	**4b**	Ph	**5a**	Me	**6n**	51
15	**1b**	Bn	H	MeO	**4b**	Ph	**5a**	Me	**6o**	63
16	**1g**	Me	H	Me	**4b**	Ph	**5a**	Me	**6p**	54
17	**1b**	Bn	H	MeO	**4c**	4-ClC_6H_4	**5a**	Me	**6q**	43
18	**1f**	Bn	MeO	Me	**4c**	4-ClC_6H_4	**5a**	Me	**6r**	37
19	**1a**	Bn	H	Me	**4d**	Bn	**5a**	Me	**6s**	0[a]

[a] *The corresponding amide **8a** (see **Table 4**) was isolated in 17 % yield along with compound **7** in 25 % yield.*

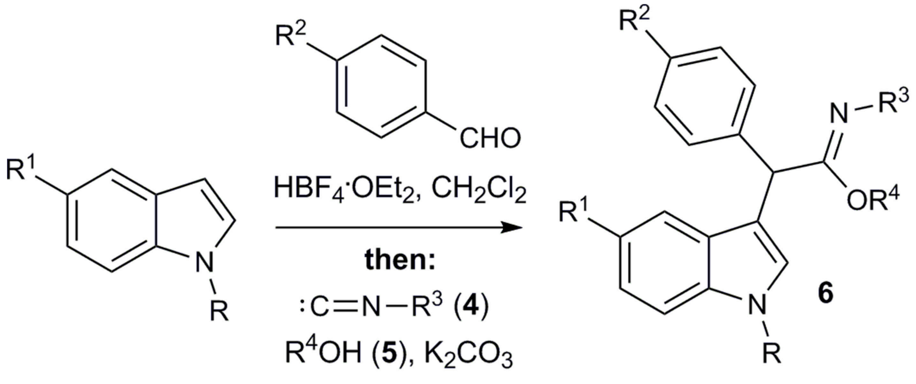

FIGURE 5 | Consecutive four-component synthesis of imidates **6**.

reversibility of the process and the lower stability of the corresponding imidate. In the case that water is present, the hydroxide ion acts as nucleophile leading to the imidic acid **B**, which is in equilibrium with the corresponding amide **8**. This last step makes the entire sequence of reactions almost irreversible.

CONCLUSIONS

We have elaborated a three-component reaction of a 3-arylidene-3*H*-indolium salt, an aromatic isocyanide and an alcohol, leading to a series of alkyl aryl(indol-3-yl)acetimidates with yields up to 87%. We have also established a consecutive four-component synthesis of the above mentioned imidates from a *N*-alkylindole, an aromatic aldehyde, an aromatic isocyanide and an alcohol. By using aqueous acetonitrile-methanol media we have expanded our method for the synthesis of aryl(indol-3-yl)acetamides. These reactions present a new practical synthetic approach to a series of compounds possessing a privileged indole scaffold and then also extend isocyanide-based MCRs by using vinylogous iminium ions.

TABLE 3 | Consecutive four-component synthesis of imidates **6**[a].

Entry	Product	R	R^1	R^2	R^3	R^4	Yield, %
1	**6b**	Bn	H	MeO	4-$MeOC_6H_4$	Me	74
2	**6e**	Me	H	MeO	4-$MeOC_6H_4$	Me	77
3	**6f**	Me	H	H	4-$MeOC_6H_4$	Me	68
4	**6g**	Me	H	Me_2N	4-$MeOC_6H_4$	Me	24
5	**6i**	Bn	Br	MeO	4-$MeOC_6H_4$	Me	40
6	**6j**	Bn	MeO	Me	4-$MeOC_6H_4$	Me	56
7	**6l**	Bn	H	MeO	4-$MeOC_6H_4$	Et	37
8	**6m**	Bn	H	MeO	4-$MeOC_6H_4$	*i*-Pr	46
9	**6n**	Bn	H	Me	Ph	Me	41
10	**6q**	Bn	H	MeO	4-ClC_6H_4	Me	36

[a] *Reaction conditions: 1.0 equiv. of aldehyde, 1.5 equiv. HBF_4OEt_2, CH_2Cl_2, 0 – 20°C then, 1.3 equiv. 4, 2.0 equiv. K_2CO_3, R^4OH (1:1 to CH_2Cl_2), rt, 12 h.*

MATERIALS AND METHODS

General

Starting reagents were purchased from commercial sources and were used without any additional purification or were prepared according to literature procedures. ^1H and ^{13}C NMR spectra were acquired on a Jeol JNM-ECA 600 spectrometer (with operating frequencies of 600 and 150 MHz, respectively) at room temperature and referenced to the residual signals of the solvent. The solvents used for NMR were DMSO-d_6 and $CDCl_3$. Chemical shifts are reported in parts per million (δ/ppm). Coupling constants are reported in Hertz (J/Hz). The peak patterns are indicated as follows: s, singlet; d, doublet; t, triplet; q, quadruplet; m, multiplet; dd, doublet of doublets and br s, broad singlet. Infrared spectra were measured on an Infralum FT-801 FT/IR instrument. The wavelengths are reported in reciprocal centimeters (νmax /cm^{-1}). Mass spectra were recorded with LCMS-8040 Triple quadrupole liquid chromatograph mass-spectrometer from Shimadzu (ESI) and Kratos MS-30 mass-spectrometer (EI, 70 eV). HRMS spectra were recorded on a Bruker MicrOTOF-Q II. Elemental analysis was performed on an Euro Vector EA-3000 elemental analyzer. The reaction progress was monitored by TLC and the spots were visualized under UV light (254 or 365 nm). Column chromatography was performed using silica gel (230–400 mesh). Melting points were determined

TABLE 4 | Synthesis of amides **8**[a].

Entry	Product	R	R^1	R^2	R^3	Yield (%)
1	**8a**	Bn	H	Me	Bn	59
2	**8b**	Bn	H	MeO	Bn	63
3	**8c**	Me	H	MeO	Bn	53
4	**8d**	Me	H	H	Bn	50
5	**8e**	Bn	Br	Me	Bn	51
6	**8f**	Bn	MeO	Me	Bn	57
7	**8g**	Bn	H	MeO	4-$MeOC_6H_4$	44
8	**8h**	Bn	H	MeO	4-ClC_6H_4	54

[a] *Reaction conditions: 1.3 equiv. **4**, 1.5 equiv. K_2CO_3, MeOH – MeCN – H_2O (1:1:0.2), r.t., 12 h.*

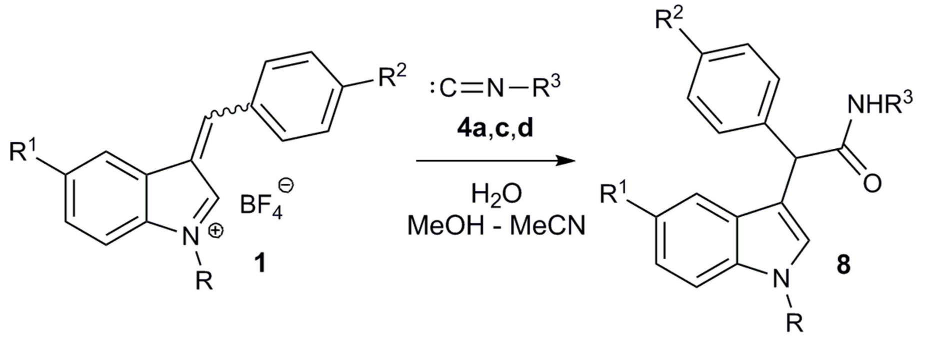

FIGURE 6 | Synthesis of amides **8**.

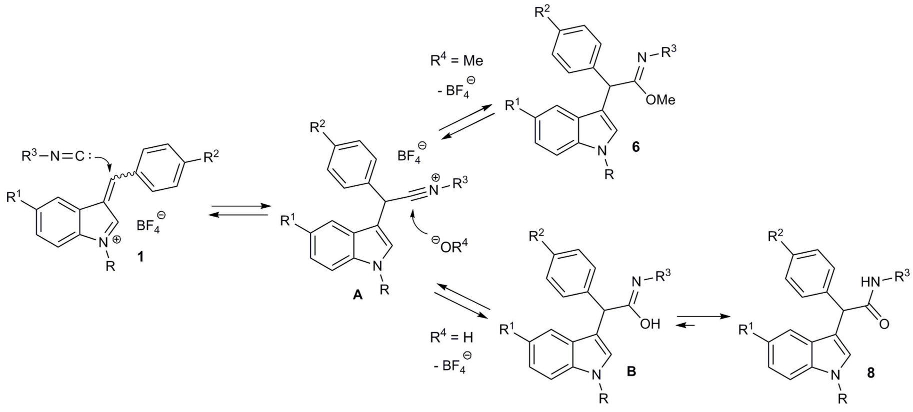

FIGURE 7 | Proposed mechanism of imidates **6** and amides **8** formation.

on a SMP-10 apparatus and were uncorrected. Solvents were distilled and dried according to standard procedures.

Synthesis of Tetrafluoroborates 1a-f

1-Benzyl-3-(4-Methylbenzylidene)-3H-Indolium Tetrafluoroborate (1a); Typical Procedure

1*H*-Indole (5.00 g, 42.7 mmol) and benzyl chloride (7.30 ml, 63.4 mmol) were dissolved in 10 ml of dry DMSO and finely ground KOH (3.5 g, 62.5 mmol) was added at 0–5°C in one portion. The reaction mixture was stirred at r.t. for 3 h and then poured into 100 mL of cold water. The product was extracted with ether (2 × 50 mL). The combined organic layers were washed with water (50 mL), brine (30 mL) and dried over anhydrous Na_2SO_4, after which the solvent was removed in vacuo. The residue was purified by flash chromatography on short column of silica gel (EtOAc – hexane, 20:1) to afford 1-benzyl-3*H*-indole (**2a**) (8.6 g, 97%) as white crystals.

1-Benzyl-1*H*-indole (**2a**) (1.00 g, 4.82 mmol) and *p*-tolualdehyde (**3a**) (4.82 mmol) were dissolved in a mixture of dry CH_2Cl_2 (5 mL) and Et_2O (5 mL). Then $HBF_4 \cdot OEt_2$ (1.00 ml, 7.35 mmol) was added dropwise at 0–5°C over a period of 2 min. The reaction mixture was allowed to warm to r.t. and stirred for 20 min. The resulting precipitate was filtered, washed thoroughly with Et_2O (5 × 20 mL) to give 1-benzyl-3-(4-methylbenzylidene)-3*H*-indolium tetrafluoroborate.

Yield: 1.78 g (93%); bright orange solid; mp 201–203°C (dec.).

IR (film): 3438, 3127, 1736, 1621, 1587, 1527, 1447, 1369, 1299, 1257, 1186, 1100, 1073, 1048, 813, 761, 711 cm^{-1}.

^{1}H NMR (600 MHz, $CDCl_3$+TFA; ∼ 3:1 *Z*/*E* diastereomeric mixture): δ = 9.17 (s, 0.67 H), 8.91 (s, 0.33 H), 8.82 (s, 0.67 H), 8.71 (s, 0.33 H), 8.32 (d, *J* = 8.1 Hz, 0.33 H), 8.01 (d, *J* = 8.0 Hz, 0.67 H), 7.97 (d, *J* = 8.1 Hz, 0.67 H), 7.91–7.85 (m, 1.33 H), 7.65–7.52 (m, 3 H), 7.50–7.36 (m, 7 H), 5.70 (s, 1.33 H), 5.60 (s, 0.67 H), 2.54 (s, 1 H), 2.49 (s, 2 H).

^{13}C NMR (150 MHz, $CDCl_3$+TFA): δ = 165.3, 160.6, 159.7, 153.4, 150.6, 149.7, 141.6, 139.9, 134.8, 134.2, 131.7, 131.4, 131.0, 130.95, 130.90, 130.6, 130.1, 129.97, 129.94, 129.86, 129.7, 129.64, 129.60, 129.2, 128.5, 128.45, 128.3, 127.09, 127.07, 125.2, 124.1, 121.2, 115.1, 115, 54.7, 54.2, 22.5, 22.3.

HRMS (TOF ES^+): *m*/*z* $[M - BF_4^-]^+$ calcd for $C_{23}H_{20}N^+$: 310.1590; found: 310.1596.

1-Benzyl-3-(4-Methoxylbenzylidene)-3H-Indolium Tetrafluoroborate (1b)

Red solid; yield 1.97 g (99% from 1.00 g 1-benzyl-1*H*-indole (**2a**)); mp 214-216°C (dec.).

IR (film): 3130, 2956, 2917, 2847, 1736, 1581, 1556, 1520, 1441, 1370, 1281, 1262, 1173, 1098, 1062, 835, 760, 710, 587 cm^{-1}.

^{1}H NMR (600 MHz, $CDCl_3$+TFA; ∼ 2.3:1 *Z*/*E* diastereomeric mixture): δ = 9.06 (s, 0.7 H), 8.75 (s, 0.7 H), 8.72 (s, 0.3 H), 8.62 (s, 0.3 H), 8.37 – 8.32 (m, 0.3 H), 8.16 (d, *J* = 9.0 Hz, 0.6 H), 8.04 (d, *J* = 8.6 Hz, 1.4 H), 7.99 (d, *J* = 8.1 Hz, 0.7 H), 7.66 – 7.52 (m, 3 H), 7.48 – 7.34 (m, 5 H), 7.22 – 7.15 (m, 2 H), 5.68 (s, 1.4 H), 5.58 (s, 0.6 H), 4.04 (s, 0.9 H), 4.01 (s, 2.1 H).

^{13}C NMR (150 MHz, $CDCl_3$+TFA): δ = 169.2, 168.3, 164.5, 159.0, 158.6, 150.9, 142.4, 139.5, 138.7, 138.5, 131.9, 131.3, 130.1, 130.0, 129.97, 129.95, 129.90, 129.13, 129.10, 129.0, 128.9, 128.5, 128.1, 127.5, 127.0, 126.9, 125.3, 124.4, 123.7, 120.7, 117.2, 116.3, 114.8, 114.5, 56.6, 56.5, 54.4, 53.9.

HRMS (TOF ES^+): *m*/*z* $[M - BF_4^-]^+$ calcd for $C_{23}H_{20}NO^+$: 326.1539; found: 326.1550.

1-Benzyl-3-Benzylidene-3H-indolium Tetrafluoroborate (1c)

Bright orange solid; yield 1.64 g (89% from 1.00 g 1-benzyl-1*H*-indole (**2a**)); mp 163-165°C (dec.).

IR (film): 3416, 3115, 1619, 1605, 1587, 1568, 1531, 1447, 1370, 1296, 1253, 1192, 1099, 1050, 826, 759, 710, 678, 599, 570 cm^{-1}.

^{1}H NMR (600 MHz, $CDCl_3$+TFA; ∼ 1.7:1 *Z*/*E* diastereomeric mixture): δ = 9.15 (s, 0.63 H), 8.93 (s, 0.37 H), 8.90 (s, 0.63 H), 8.74 (s, 0.37 H), 8.29 (d, *J* = 7.7 Hz, 0.37 H), 8.04 (d, *J* = 7.7 Hz, 0.63 H), 8.02 (d, *J* = 8.0 Hz, 0.76 H), 7.92 (d, *J* = 7.7 Hz, 1.26 H), 7.80 – 7.72 (m, 1 H), 7.69 – 7.56 (m, 5 H), 7.48 – 7.36 (m, 5 H), 5.72 (s, 1.26 H), 5.62 (s, 0.76 H).

^{13}C NMR (150 MHz, $CDCl_3$+TFA): δ = 165.0, 161.4, 159.6, 154.5, 142.9, 140.4, 136.9, 136.4, 134.1, 133.72, 133.70, 133.4, 133.3, 131.03, 131.0, 130.7, 130.6, 130.5, 130.4, 130.3, 130.2, 130.1, 130.03, 130.0, 129.97, 128.7, 128.6, 125.4, 128.2, 125.1, 124.3, 121.6, 115.3, 115.2, 55.0, 54.5.

HRMS (TOF ES$^+$): *m/z* $[M - BF_4^-]^+$ calcd for $C_{22}H_{18}N^+$: 296.1434; found: 296.1441.

1-Benzyl-5-Bromo-3-(4-Methylbenzylidene)-3H-Indolium Tetrafluoroborate (1d)

Bright orange solid; yield 1.35 g (81% from 1.00 g 1-benzyl-5-bromo-1*H*-indole (**2b**)); mp 220-222°C (dec.).

IR (film): 3126, 1736, 1620, 1587, 1526, 1448, 1424, 1372, 1319, 1259, 1188, 1104, 1051, 802, 772, 743, 714, 653, 629 cm^{-1}.

^{1}H NMR (600 MHz, $CDCl_3$+TFA; ∼ 2.3:1 *Z*/*E* diastereomeric mixture): δ = 9.13 (s, 0.70 H), 8.85 (s, 0.70 H), 8.83 (s, 0.30 H), 8.76 (s, 0.30 H), 8.49 (d, *J* = 2.0 Hz, 0.30 H), 8.18 (d, *J* = 2.0 Hz, 0.70 H), 7.99 (d, *J* = 8.1 Hz, 0.60 H), 7.90 (d, *J* = 8.1 Hz, 1.40 H), 7.75 (dd, *J* = 8.7 Hz, 1.7 Hz, 0.30 H), 7.71 (dd, *J* = 8.7 Hz, 1.7 Hz, 0.70 H), 7.56 (d, *J* = 8.1 Hz, 0.60 H), 7.52 (d, *J* = 8.1 Hz, 1.70 H), 7.50 – 7.42 (m, 3.70 H), 7.42 – 7.36 (m, 2 H), 5.71 (s, 1.40 H), 5.62 (s, 0.60 H), 2.59 (s, 0.90 H), 2.54 (s, 2.10 H).

^{13}C NMR (150 MHz, $CDCl_3$+TFA): δ = 167.1, 161.3, 160.3, 153.2, 152.3, 151.4, 141.6, 138.9, 135.4, 134.8, 133.7, 133.0, 132.2, 131.7, 131.58, 131.57, 131.5, 131.1, 130.7, 130.5, 130.4, 130.24, 130.2, 128.7, 128.4, 128.2, 127.2, 126.1, 124.5, 124.4, 124.2, 117.5, 116.5, 116.4, 55.3, 54.7, 22.4, 22.2.

HRMS (TOF ES$^+$): *m/z* $[M - BF_4^-]^+$ calcd for $C_{23}H_{19}BrN^+$: 388.0695; found: 388.0701.

1-Benzyl-5-Bromo-3-(4-Methoxylbenzylidene)-3*H*-Indolium Tetrafluoroborate (1e)

Red orange solid; yield 1.46 g (85% from 1.00 g 1-benzyl-5-bromo-1*H*-indole (**2b**)); mp 226-228°C (dec.).

IR (film): 3464, 3129, 2841, 1582, 1554, 1520, 1447, 1429, 1375, 1319, 1281, 1178, 1103, 1051, 888, 835, 799, 773, 716, 629, 595, 556 cm^{-1}.

^{1}H NMR (600 MHz, $CDCl_3$+TFA; ∼ 3.3:1 *Z*/*E* diastereomeric mixture): δ = 9.07 (s, 0.77 H), 8.73 (s, 0.23 H), 8.72 (s, 0.77 H), 8.68 (s, 0.23 H), 8.45 (d, *J* = 1.5 Hz, 0.23 H), 8.16 (d, *J* = 9.1 Hz, 0.46 H),), 8.13 (d, *J* = 1.5 Hz, 0.77 H),), 8.08 (d, *J* = 9.1 Hz, 1.54 H), 7.71 (dd, *J* = 8.6 Hz, 1.5 Hz, 0.23 H), 7.64 (dd, *J* = 8.6 Hz, 1.5 Hz, 0.77 H), 7.48 (d, *J* = 8.6 Hz, 0.23 H), 7.46 – 7.39 (m, 3.77 H), 7.38 – 7.31 (m, 2 H), 7.24 (d, *J* = 8.9 Hz, 0.46 H), 7.21 (d, *J* = 8.9 Hz, 0.46 H), 5.67 (s, 1.54 H), 5.57 (s, 0.46 H), 4.07 (s, 0.69 H), 4.04 (s, 2.31 H).

^{13}C NMR (150 MHz, $CDCl_3$+TFA): δ = 170.3, 169.3, 165.8, 159.9, 158.3, 150.6, 141.0, 139.5, 139.1, 138.1, 132.8, 132.0, 131.7, 131.2, 130.7, 130.6, 130.3, 130.1, 130.0, 128.4, 128.2, 128.1, 127.5, 127.1, 127.0, 126.5, 125.5, 123.8, 123.2, 123.0, 117.6, 116.8, 116.0, 115.9, 56.8, 56.7, 54.7, 54.1.

HRMS (TOF ES$^+$): *m/z* $[M - BF_4^-]^+$ calcd for $C_{23}H_{19}BrNO^+$: 404.0645; found: 404.0651.

1-Benzyl-5-Methoxy-3-(4-Methylbenzylidene)-3*H*-Indolium Tetrafluoroborate (1f)

Dark violet solid; yield 1.50 g (83% from 1.00 g 1-benzyl-5-methoxy-1*H*-indole (**2c**)); mp 212-214°C (dec.).

IR (film): 3130, 2947, 1619, 1587, 1526, 1482, 1444, 1372, 1298, 1263, 1237, 1189, 1099, 1051, 916, 858, 808, 754, 705, 645 cm^{-1}.

^{1}H NMR (600 MHz, $CDCl_3$+TFA; ∼ 2.7:1 *Z*/*E* diastereomeric mixture): δ = 8.89 (s, 0.73 H), 8.78 (s, 0.73 H), 8.64 (s, 0.27 H), 8.59 (s, 0.27 H), 7.95 (d, *J* = 8.1 Hz, 0.54 H), 7.87 (d, *J* = 2.5 Hz, 0.27 H),), 7.82 (d, *J* = 8.1 Hz, 1.46 H),), 7.54 – 7.51 (m, 1 H), 7.50 – 7.41 (m, 5.73 H), 7.41 – 7.34 (m, 2 H), 7.14 (dd, *J* = 9.1 Hz, 2.5 Hz, 0.27 H), 7.10 (dd, *J* = 9.1 Hz, 2.5 Hz, 0.73 H), 5.63 (s, 1.46 H), 5.55 (s, 0.54 H), 3.96 (s, 2.19 H), 3.89 (s, 0.81 H), 2.54 (s, 0.81 H), 2.50 (s, 2.19 H).

^{13}C NMR (150 MHz, $CDCl_3$+TFA): δ = 164.3, 158.9, 158.7, 151.3, 150.4, 149.6, 136.8, 134.6, 134.1, 133.8, 131.8, 131.4, 131.2, 131.0, 130.9, 130.8, 130.7, 130.6, 130.3, 130.2, 130.1, 130.0, 129.3, 128.6, 128.3, 127.3, 127.2, 127.0, 116.8, 116.2, 116.13, 116.09, 110.0, 106.0, 56.44, 56.36, 55.0, 54.4, 22.4, 22.2.

HRMS (TOF ES$^+$): *m/z* $[M - BF_4^-]^+$ calcd for $C_{24}H_{22}NO^+$: 340.1696; found: 340.1701.

Synthesis of Imidates 6

Three-Component Synthesis of Imidates 6; General Procedure (GP1)

An isocyanide **4** (0.65 mmol) was dissolved in a mixture of abs. alcohol (1 mL) and MeCN (1 mL). A salt **1** (0.5 mmol) and K_2CO_3 (0.1 g, 0.75 mmol) were then added. The reaction mixture was stirred at r.t. for 12 h and concentrated in vacuo. The residue was dissolved in EtOAc (50 mL), washed with $NaHCO_3$ (2 × 25 mL), brine (20 mL), and dried over anhydrous Na_2SO_4. The EtOAc was evaporated in vacuo. The residue was chromatographed on a column with silica gel with EtOAc–hexane.

Consecutive Four-Component Synthesis of Imidates 6; General Procedure (GP2)

N-Alkylindole (0.5 mmol) and aromatic aldehyde (0.5 mmol) were dissolved in dry CH_2Cl_2 (3 mL). $HBF_4 \cdot OEt_2$ (0.1 ml, 0.75 mmol) was then added dropwise at 0–5°C over a period of 2 min. The reaction mixture was allowed to warm to r.t. and stirred for additional 20 min. Then K_2CO_3 (0.14 g, 1.0 mmol), anhydrous alcohol (3 ml) and isocyanide **4** (0.65 mmol) were added. The reaction mixture was stirred at r.t. for 12 h and concentrated in vacuo. The residue was dissolved in EtOAc (50 mL), washed with $NaHCO_3$ (2 × 25 mL), brine (20 mL) and dried over anhydrous Na_2SO_4. The EtOAc was evaporated in vacuo. The residue was chromatographed on a column with silica gel with EtOAc–hexane.

Methyl 2-(1-Benzyl-1*H*-Indol-3-yl)-*N*-(4-Methoxyphenyl)-2-(*p*-tolyl)acetimidate (6a)

Yield, obtained by following GP1: 154 mg (65%).

Yellowish oil; $R_f = 0.47$ (EtOAc–hexane, 1:6).

IR (film): 3028, 2925, 2834, 1733, 1661, 1609, 1583, 1506, 1465, 1354, 1303, 1238, 1178, 1032, 909, 831, 740, 696, 636 cm^{-1}.

^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.36 – 7.23 (m, 5H), 7.19 – 7.13 (m, 3H), 7.12 – 7.07 (m, 4H), 7.05 – 6.99 (m, 2H), 6.84 (d, *J* = 9.1 Hz, 2H), 6.74 (d, *J* = 9.1 Hz, 2H), 5.42 (s, 1H), 5.37 – 5.29 (m, 2H), 3.84 (s, 3H), 3.80 (s,3H), 2.33 (s, 3H).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 163.6, 155.8, 141.8, 137.7, 137.1, 136.7, 136.4, 129.1 (2C), 128.8 (2C), 128.4 (2C), 128.0, 127.7, 127.4, 126.7 (2C), 122.4 (2C), 122.0, 119.7, 119.4, 114.4 (2C), 114.0, 109.9, 55.6, 53.7, 50.1, 42.7, 21.2.

MS (ESI): m/z = 475 [M + H]$^+$

HRMS (TOF ES$^+$): m/z [M + H]$^+$ calcd for $C_{32}H_{31}N_2O_2^+$: 475.2380; found: 475.2375.

Methyl 2-(1-Benzyl-1*H*-indol-3-yl)-*N*,2-bis(4-methoxyphenyl)acetimidate (6b)

Yield, obtained by following GP1: 206 mg (84%).

Yield, obtained by following GP2: 181 mg (74%).

Yellowish oil; R_f = 0.33 (EtOAc–hexane, 1:5).

IR (film): 3029, 2997, 2939, 2834, 1734, 1656, 1609, 1583, 1508, 1465, 1301, 1238, 1177, 1104, 1034, 908, 834, 741, 696, 636 cm^{-1}.

^{1}H NMR (600 MHz, CDCl$_3$): δ = 7.36 – 7.23 (m, 5H), 7.21 – 7.14 (m, 3H), 7.12 (d, *J* = 7.0 Hz, 2H), 7.07 – 7.00 (m, 2H), 6.88 – 6.82 (m, 4H), 6.79 – 6.74 (m, 2H), 5.41 (s, 1H), 5.37 – 5.28 (m, 2H), 3.86 (s, 3H), 3.81 (s, 3H), 3.80 (s, 3H).

^{13}C NMR (150 MHz, CDCl$_3$): δ = 163.7, 158.5, 155.8, 141.8, 137.7, 136.78, 132.2, 129.6 (2C), 128.9 (2C), 128.0, 127.7, 127.4, 126.7 (2C), 122.4 (2C), 122.0, 119.7, 119.4, 114.5(2C), 114.3, 113.8 (2C), 109.9, 55.6, 55.3, 53.67, 50.2, 42.4.

MS (ESI): m/z = 491 [M + H]$^+$

HRMS (TOF ES$^+$): m/z [M + H]$^+$ calcd for $C_{32}H_{31}N_2O_3^+$: 491.2329; found: 491.2337.

Methyl 2-(1-Benzyl-1*H*-Indol-3-yl)-*N*-(4-Methoxyphenyl)-2-Phenylacetimidate (6c)

Yield, obtained by following GP1: yield 129 mg (56%).

Yellowish oil; R_f = 0.43 (EtOAc–hexane, 1:5).

IR (film): 3058, 3027, 2931, 2833, 2391, 1735, 1662, 1605, 1506, 1466, 1334, 1301, 1238, 1178, 1031, 908, 833, 738, 698, 627 cm^{-1}.

^{1}H NMR (600 MHz, CDCl$_3$): δ = 7.32 – 7.29 (m, 2H), 7.28 – 7.25 (m, 5H), 7.24 – 7.22 (m, 3H), 7.15 (dd, *J* = 8.0, 7.2 Hz, 1H), 7.10 (d, *J* = 7.6 Hz, 2H), 7.03 – 6.99 (m, 2H), 6.82 (d, *J* = 8.6 Hz, 2H), 6.73 (d, *J* = 8.6 Hz, 2H), 5.44 (s, 1H), 5.35 – 5.27 (m, 2H), 3.83 (s, 3H), 3.79 (s, 3H).

^{13}C NMR (150 MHz, CDCl$_3$): δ = 163.4, 155.8, 141.8, 140.2, 137.7, 136.7, 128.9 (2C), 128.5 (2C), 128.4 (2C), 128.1, 127.7, 127.4, 126.8, 126.7 (2C), 122.4 (2C), 122.0, 119.7, 119.4, 114.5 (2C), 113.8, 109.9, 55.6, 53.7, 50.2, 43.1.

MS (ESI): m/z = 461 [M + H]$^+$

HRMS (TOF ES$^+$): m/z [M + H]$^+$ calcd for $C_{31}H_{29}N_2O_2^+$: 461.2224; found: 461.2217.

Methyl *N*-(4-Methoxyphenyl)-2-(1-Methyl-1*H*-Indol-3-yl)-2-(*p*-tolyl)acetimidate (6d)

Yield, obtained by following GP1: yield 101 mg (51%)

Brownish oil; R_f = 0.50 (EtOAc–hexane, 1:5).

IR (film): 3048, 3000, 2941, 2833, 1663, 1505, 1465, 1372, 1237, 1179, 1031, 909, 833, 773, 740, 644 cm^{-1}.

^{1}H NMR (600 MHz, CDCl$_3$): δ = 7.29 (d, *J* = 8.1 Hz, 1H), 7.24 (d, *J* = 8.1 Hz, 1H), 7.22 – 7.18 (m, 1H), 7.12 (d, *J* = 8.0 Hz, 2H), 7.08 (d, *J* = 8.0 Hz, 2H), 7.01 (m, 1H), 6.89 (s, 1H), 6.83 (d, *J* = 8.9 Hz, 2H), 6.73 (d, *J* = 8.9 Hz, 2H), 5.37 (s, 1H), 3.84 (s, 3H), 3.79 (s,3H), 3.76 (s, 3H), 2.32 (s, 3H).

^{13}C NMR (150 MHz, CDCl$_3$): δ = 163.6, 155.8, 141.8, 137.3, 137.0, 136.3, 129.1 (2C), 128.39, 128.37 (2C), 127.1, 122.4 (2C), 121.7, 119.4, 119.1, 114.4 (2C), 113.4, 109.3, 55.6, 53.7, 42.6, 32.9, 21.2.

MS (ESI): m/z = 399 [M + H]$^+$

HRMS (TOF ES$^+$): m/z [M + H]$^+$ calcd for $C_{26}H_{27}N_2O_2^+$: 399.2067; found: 399.2035.

Methyl *N*,2-bis(4-Methoxyphenyl)-2-(1-Methyl-1*H*-Indol-3-yl)acetimidate (6e)

Yield, obtained by following GP1: 180 mg (87%).

Yield, obtained by following GP2: 160 mg (77%).

Brownish oil; R_f = 0.37 (EtOAc–hexane, 1:5).

IR (film): 3048, 2998, 2943, 2834, 2391, 1737, 1661, 1609, 1583, 1508, 1464, 1440, 1329, 1239, 1178, 1032, 908, 834, 740, 634 cm^{-1}.

^{1}H NMR (600 MHz, CDCl$_3$): δ = 7.29 (d, *J* = 8.1 Hz, 1H), 7.23 (d, *J* = 8.1 Hz, 1H), 7.22 −7.19 (m, 1H), 7.14 (d, *J* = 9.1 Hz, 2H), 7.04 – 6.99 (m, 1H), 6.87 (s, 1H), 6.82 (d, *J* = 8.9 Hz, 2H), 6.80 (d, *J* = 8.9 Hz, 2H), 6.72 (d, *J* = 9.1 Hz, 2H), 5.34 (s, 1H), 3.84 (s, 3H), 3.79 (s, 3H), 3.78 (s, 3H), 3.76 (s, 3H).

^{13}C NMR (150 MHz, CDCl$_3$): δ = 163.7, 158.4, 155.7, 141.8, 137.1, 132.4, 129.5 (2C), 128.3, 127.1, 122.4 (2C), 121.7, 119.4, 119.1, 114.4 (2C), 113.7 (2C), 113.6, 109.3, 55.6, 55.3, 53.7, 42.3, 32.9.

MS (ESI): m/z = 415 [M + H]$^+$

HRMS (TOF ES$^+$): m/z [M + H]$^+$ calcd for $C_{26}H_{27}N_2O_3^+$: 415.2016; found: 415.2025.

Methyl *N*-(4-Methoxyphenyl)-2-(1-Methyl-1*H*-Indol-3-yl)-2-Phenylacetimidate (6f)

Yield, obtained by following GP1: 150 mg (78%).

Yield, obtained by following GP2: 131 mg (68%).

Brownish oil; R_f = 0.50 (EtOAc–hexane, 1:3).

IR (film): 3108, 2996, 2938, 2901, 2834, 1738, 1664, 1604, 1547, 1503, 1439, 1372, 1304, 1239, 1180, 1155, 1105, 1032, 905, 845, 799, 743, 718, 650 cm^{-1}.

^{1}H NMR (600 MHz, CDCl$_3$): δ = 7.30 (d, *J* = 8.2 Hz, 1H), 7.29 – 7.25 (m, 2H), 7.24 – 7.19 (m, 5H), 7.01 (m, 1H), 6.90 (s, 1H), 6.83 (d, *J* = 8.6 Hz, 2H), 6.73 (d, *J* = 8.6 Hz, 2H), 5.41 (s, 1H), 3.85 (s, 3H), 3.79 (s, 3H), 3.76 (s, 3H).

^{13}C NMR (150 MHz, CDCl$_3$): δ = 163.4, 155.8, 141.8, 140.3, 137.1, 128.49 (2C), 128.45, 128.4 (2C), 127.1, 126.8, 122.4 (2C), 121.8, 119.4, 119.1, 114.4 (2C), 113.2, 109.3, 55.6, 53.7, 43.0, 32.9.

MS (ESI): m/z = 385 [M + H]$^+$

HRMS (TOF ES$^+$): m/z [M + H]$^+$ calcd for $C_{25}H_{25}N_2O_2^+$: 385.1911; found: 385.1911.

Methyl 2-(4-(Dimethylamino)phenyl)-N-(4-Methoxyphenyl) -2-(1-Methyl-1H-indol-3-yl) acetimidate (6g)

Yield, obtained by following GP1: 109 mg (51%).

Yield, obtained by following GP2: 51 mg (24%).

Brownish oil; R_f = 0.44 (EtOAc–hexane, 1:5).

IR (film): 3059, 2927, 2852, 1759, 1703, 1661, 1602, 1512, 1464, 1351, 1237, 1157, 1031, 945, 825, 740, 607 cm^{-1}.

^{1}H NMR (600 MHz, CDCl$_3$): δ = 7.29 – 7.26 (m, 2H), 7.22 – 7.18 (m, 1H), 7.12 (d, *J* = 8.6 Hz, 2H), 6.99 – 7.04 (m, 1H), 6.88 (s, 1H), 6.83 (d, *J* = 8.6 Hz, 2H), 6.74 (d, *J* = 8.6 Hz, 2H), 6.73 – 6.66 (m, 2H), 5.31 (s, 1H), 3.83 (s, 3H), 3.79 (s, 3H), 3.75 (s, 3H), 2.93 (s, 6H).

^{13}C NMR (150 MHz, CDCl$_3$): δ = 164.0, 155.8, 141.9, 137.1, 129.5, 129.3, 128.4 (2C), 127.2, 122.5 (2C), 121.8, 121.7, 119.5, 119.0, 114.4 (2C), 114.0, 112.8 (2C), 109.3, 55.6, 53.7, 42.2, 41.0 (2C), 32.9.

MS (ESI): $m/z = 428$ [M + H]$^+$

HRMS (TOF ES$^+$): m/z [M + H]$^+$ calcd for $C_{27}H_{30}N_3O_2^+$: 428.2333; found: 428.2208.

Methyl 2-(1-Benzyl-5-Bromo-1H-Indol-3-yl)-N-(4-Methoxyphenyl)-2-(p-tolyl)acetimidate (6h)

Yield, obtained by following GP1: 130 mg (47%)

Brown oil; $R_f = 0.47$ (EtOAc–hexane, 1:7).

IR (film): 3030, 2941, 2833, 1733, 1661, 1607, 1505, 1468, 1282, 1237, 1176, 1103, 1033, 909, 874, 828, 793, 765, 732, 697, 641 cm^{-1}.

^{1}H NMR (600 MHz, CDCl$_3$): δ = 7.36 (d, J = 2.0 Hz, 1H), 7.34 – 7.27 (m, 3H), 7.21 (dd, J = 8.6, 2.0 Hz, 1H), 7.12 – 7.07 (m, 5H), 7.06 (d, J = 7.7 Hz, 2H), 7.02 (s, 1H), 6.85 (d, J = 9.1 Hz, 2H), 6.71 (d, J = 9.1 Hz, 2H), 5.33 (s, 1H), 5.32 – 5.24 (m, 2H), 3.83 (s, 3H), 3.81 (s, 3H), 2.33 (s, 3H).

^{13}C NMR (150 MHz, CDCl$_3$): δ = 163.3, 155.9, 141.6, 137.2, 136.7, 136.6, 135.3, 129.3 (2C), 129.2, 129.1, 128.9 (2C), 128.3 (2C), 127.9, 126.6 (2C), 124.9, 122.4 (2C), 122.3, 114.5 (2C), 113.6, 112.9, 111.5, 55.6, 53.8, 50.4, 42.5, 21.2.

MS (ESI): $m/z = 553$ [M + H]$^+$

HRMS (TOF ES$^+$): m/z [M + H]$^+$ calcd for $C_{32}H_{30}BrN_2O_2^+$: 553.1485; found: 553.1505.

Methyl 2-(1-Benzyl-5-Bromo-1H-Indol-3-yl)-N,2-bis(4-Methoxyphenyl)acetimidate (6i)

Yield, obtained by following GP1: 148 mg (52%).

Yield, obtained by following GP2: 114 mg (40%).

Brownish oil; $R_f = 0.60$ (EtOAc–hexane, 1:5).

IR (film): 3030, 2996, 2943, 2834, 1734, 1662, 1608, 1508, 1467, 1354, 1238, 1176, 1104, 1033, 908, 832, 734, 697, 634 cm^{-1}.

^{1}H NMR (600 MHz, CDCl$_3$): δ = 7.37 (d, J = 1.8 Hz, 1H), 7.33 – 7.25 (m, 3H), 7.20 (dd, J = 8.6, 1.8 Hz, 1H), 7.13 (d, J = 8.6 Hz, 2H), 7.08 (d, J = 8.6 Hz, 1H), 7.06 – 7.03 (m, 2H), 7.00 (s, 1H), 6.84 (d, J = 8.6 Hz, 2H), 6.82 (d, J = 9.1 Hz, 2H), 6.71 (d, J = 9.1 Hz, 2H), 5.31 (s, 1H), 5.31 – 5.23 (m, 2H), 3.82 (s, 3H), 3.80 (s, 3H), 3.78 (s, 3H).

^{13}C NMR (150 MHz, CDCl$_3$): δ = 163.3, 158.6, 155.9, 141.6, 137.2, 135.4, 131.7, 129.4 (2C), 129.1, 129.0, 128.9 (2C), 127.9, 126.6 (2C), 124.9, 122.3 (2C), 122.2, 114.5 (2C), 113.9 (2C), 113.8, 112.9, 111.4, 55.6, 55.3, 53.7, 50.4, 42.1.

MS (ESI): $m/z = 569$ [M + H]$^+$

HRMS (TOF ES$^+$): m/z [M + H]$^+$ calcd for $C_{32}H_{30}BrN_2O_3^+$: 569.1434; found: 569.1412.

Methyl 2-(1-Benzyl-5-Methoxy-1H-Indol-3-yl)-N-(4-Methoxyphenyl)-2-(p-tolyl)acetimidate (6j)

Yield, obtained by following GP1: 179 mg (71%).

Yield, obtained by following GP2: 141 mg (56%).

Brown oil; yield; $R_f = 0.56$ (EtOAc–hexane, 1:5).

IR (film): 3030, 2994, 2939, 2833, 1734, 1661, 1621, 1578, 1506, 1487, 1452, 1288, 1238, 1176, 1103, 1030, 901, 830, 774, 704 cm^{-1}.

^{1}H NMR (600 MHz, CDCl$_3$): δ = 7.31 – 7.25 (m, 3H), 7.15 (d, J = 8.1 Hz, 2H), 7.12 – 7.05 (m, 5H), 6.97 (s, 1H), 6.83 (d, J = 9.1 Hz, 2H), 6.79 (dd, J = 9.1, 2.5 Hz, 1H), 6.75 (d, J = 9.1 Hz, 2H), 6.70 (d, J = 2.5 Hz, 1H), 5.36 (s, 1H), 5.30 – 5.22 (m, 2H), 3.83 (s, 3H), 3.79 (s, 3H), 3.72 (s, 3H), 2.33 (s, 3H).

^{13}C NMR (150 MHz, CDCl$_3$): δ = 163.6, 155.8, 154.0, 141.9, 137.8, 137.80, 137.1, 136.4, 131.9, 129.1 (2C), 128.8 (2C), 128.6, 128.4 (2C), 127.8, 126.6 (2C), 122.5 (2C), 114.4 (2C), 113.5, 112.2, 110.7, 101.2, 55.8, 55.6, 53.7, 50.4, 42.6, 21.2.

MS (ESI): $m/z = 505$ [M + H]$^+$

HRMS (TOF ES$^+$): m/z [M + H]$^+$ calcd for $C_{33}H_{33}N_2O_3^+$: 505.2486; found: 505.2461.

Ethyl 2-(1-Benzyl-1H-Indol-3-yl)-N-(4-Methoxyphenyl)-2-(p-tolyl)acetimidate (6k)

Yield, obtained by following GP1: 129 mg (53%)

Brownish oil; $R_f = 0.71$ (EtOAc–hexane, 1:5).

IR (film): 3030, 2976, 2946, 2901, 2833, 1732, 1656, 1610, 1505, 1466, 1357, 1334, 1306, 1236, 1178, 1103, 1036, 958, 834, 741, 696 cm^{-1}.

^{1}H NMR (600 MHz, CDCl$_3$): δ = 7.34 – 7.23 (m, 5H), 7.17 – 7.13 (m, 3H), 7.11 (d, J = 8.1 Hz, 2H), 7.08 (d, J = 8.1 Hz, 2H), 7.05 (s, 1H), 6.99 – 7.00 (m, 1H), 6.83 (d, J = 9.1 Hz, 2H), 6.73 (d, J = 9.1 Hz, 2H), 5.40 (s, 1H), 5.31 (s, 2H), 4.34 – 4.27 (m, 2H), 3.80 (s, 3H), 2.33 (s, 3H), 1.26 (t, J = 7.1 Hz, 3H).

^{13}C NMR (150 MHz, CDCl$_3$): δ = 162.9, 155.7, 142.1, 137.7, 137.4, 136.7, 136.2, 129.0 (2C), 128.8 (2C), 128.4 (2C), 127.9, 127.7, 127.5, 126.8 (2C), 122.4 (2C), 121.9, 119.8, 119.2, 114.4 (2C), 114.2, 109.7, 61.8, 55.6, 50.1, 42.6, 21.1, 14.2.

MS (ESI): $m/z = 489$ [M + H]$^+$

HRMS (TOF ES$^+$): m/z [M + H]$^+$ calcd for $C_{33}H_{33}N_2O_2^+$: 489.2537; found: 489.2553.

Ethyl 2-(1-Benzyl-1H-Indol-3-yl)-N,2-bis(4-Methoxyphenyl)acetimidate (6l)

Yield, obtained by following GP1: 118 mg (47%).

Yield, obtained by following GP2: 93 mg (37%).

Brownish oil; $R_f = 0.71$ (EtOAc–hexane, 1:3).

IR (film): 3031, 2930, 2834, 1727, 1658, 1609, 1508, 1465, 1301, 1238, 1177, 1104, 1036, 958, 834, 741, 696, 637 cm^{-1}.

^{1}H NMR (600 MHz, CDCl$_3$): δ = 7.32 – 7.28 (m, 2H), 7.27 – 7.25 (m, 2H), 7.23 (d, J = 8.6 Hz, 1H), 7.16 (d, J = 8.4 Hz, 2H), 7.16 – 7.12 (m, 1H), 7.09 (d, J = 8.1 Hz, 2H), 7.02 (s, 1H), 7.02 – 6.98 (m, 1H), 6.81 (d, J = 8.6 Hz, 2H), 6.79 (d, J = 8.6 Hz, 2H), 6.71 (d, J = 8.6 Hz, 2H), 5.35 (s, 1H), 5.30 (s, 2H), 4.32 – 4.21 (m, 2H), 3.79 (s, 3H), 3.77 (s, 3H), 1.24 (t, J = 7.1 Hz, 3H).

^{13}C NMR (150 MHz, CDCl$_3$): δ = 163.0, 158.4, 155.7, 142.0, 137.7, 136.7, 132.5, 129.5 (2C), 128.8 (2C), 127.8, 127.7, 127.4, 126.7 (2C), 122.4 (2C), 121.9, 119.8, 119.2, 114.4 (2C), 114.3, 113.7 (2C), 109.8, 61.8, 55.6, 55.3, 50.1, 42.3, 14.2.

MS (ESI): $m/z = 505$ [M + H]$^+$

HRMS (TOF ES$^+$): m/z [M + H]$^+$ calcd for $C_{33}H_{33}N_2O_3^+$: 505.2486; found: 505.2506.

Isopropyl 2-(1-Benzyl-1*H*-Indol-3-yl)-*N*,2-bis(4-Methoxyphenyl)acetimidate (6m)

Yield, obtained by following GP1: 145 mg (56%).

Yield, obtained by following GP2: 119 mg (46%).

Brownish oil; yield; $R_f = 0.43$ (EtOAc–hexane, 1:8).

IR (film): 3056, 2933, 2837, 2736, 1683, 1654, 1600, 1577, 1509, 1465, 1302, 1250, 1160, 1178, 1108, 1030, 976, 834, 742, 698 cm^{-1}.

^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.35 – 7.29 (m, 2H), 7.28 – 7.25 (m, 2H), 7.23 (d, J = 8.2 Hz, 1H), 7.15 (d, J = 9.1 Hz, 2H), 7.13 – 7.08 (m, 3H), 7.03 (s, 1H), 7.02 – 6.98 (m, 1H), 6.81 (d, J = 8.6 Hz, 2H), 6.78 (d, J = 8.6 Hz, 2H), 6.70 (d, J = 9.1 Hz, 2H), 5.34 (s, 1H), 5.33 – 5.26 (m, 2H), 5.23 – 5.18 (m, 1H), 3.79 (s, 3H), 3.77 (s, 3H), 1.22 (d, J = 6.2 Hz, 3H), 1.17 (d, J = 6.2 Hz, 3H).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 162.1, 158.3, 155.6, 142.2, 137.7, 136.6, 132.7, 129.5 (2C), 128.8 (2C), 127.8, 127.7, 127.5, 126.8 (2C), 126.5, 122.3 (2C), 121.8, 119.8, 119.1, 114.4 (2C), 113.6 (2C), 109.7, 68.0, 55.6, 55.3, 50.1, 42.2, 21.7, 21.6.

MS (ESI): $m/z = 519$ $[M + H]^+$

HRMS (TOF ES$^+$): m/z $[M + H]^+$ calcd for $C_{34}H_{35}N_2O_3^+$: 519.2642; found: 519.2623.

Methyl 2-(1-Benzyl-1*H*-Indol-3-yl)-*N*-Phenyl-2-(*p*-tolyl)acetimidate (6n)

Yield, obtained by following GP1: 113 mg (51%).

Yield, obtained by following GP2: 91 mg (41%).

Orange oil; $R_f = 0.41$ (EtOAc–hexane, 1:10).

IR (film): 3055, 3028, 2941, 2861, 1665, 1595, 1546, 1511, 1466, 1334, 1249, 1178, 1072, 1017, 908, 834, 740, 695 cm^{-1}.

^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.34 – 7.29 (m, 2H), 7.28 – 7.25 (m, 3H), 7.25 – 7.22 (m, 2H), 7.15 – 7.11 (m, 3H), 7.10 – 7.03 (m, 5H), 7.02 – 6.98 (m, 2H), 6.79 (dd, J = 8.4, 1.1 Hz, 2H), 5.35 (s, 1H), 5.34 – 5.27 (m, 2H), 3.84 (s, 3H), 2.32 (s, 3H).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 163.1, 148.6, 137.7, 137.0, 136.7, 136.40, 129.1 (2C), 129.1 (2C), 128.8 (2C), 128.4 (2C), 128.0, 127.6, 127.4, 126.7 (2C), 123.1, 121.9, 121.5 (2C), 119.7, 119.4, 113.9, 109.9, 53.7, 50.1, 42.9, 21.2.

MS (ESI): $m/z = 445$ $[M + H]^+$

HRMS (TOF ES$^+$): m/z $[M + H]^+$ calcd for $C_{31}H_{29}N_2O^+$: 445.2274; found: 445.2250.

Methyl 2-(1-Benzyl-1*H*-Indol-3-yl)-2-(4-Methoxyphenyl)-*N*-Phenylacetimidate (6o)

Yield, obtained by following GP1: 145 mg (63%).

Orange oil; $R_f = 0.66$ (EtOAc–hexane, 1:5).

IR (film): 3030, 2928, 2837, 1738, 1664, 1594, 1510, 1465, 1303, 1247, 1175, 1031, 740 cm^{-1}.

^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.33 −7.29 (m, 2H), 7.28 – 7.21 (m, 5H), 7.16 – 7.12 (m, 3H), 7.10 – 7.07 (m, 2H), 7.07 – 7.03 (m, 1H), 7.00 (ddd, J = 8.1, 7.0, 1.0 Hz, 1H), 6.97 (s, 1H), 6.80 (d, J = 8.6 Hz, 2H), 6.79 (d, J = 8.6 Hz, 2H), 5.34 – 5.26 (m, 3H), 3.83 (s, 3H), 3.78 (s, 3H).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 163.1, 158.5, 148.6, 137.7, 136.8, 132.1, 129.5 (2C), 129.1 (2C), 128.8 (2C), 127.9, 127.6, 127.3, 126.7 (2C), 123.1, 122.0, 121.5 (2C), 119.7, 119.4, 114.2, 113.8 (2C), 109.9, 55.3, 53.7, 50.1, 42.6.

MS (ESI): $m/z = 461$ $[M + H]^+$

HRMS (TOF ES$^+$): m/z $[M + H]^+$ calcd for $C_{31}H_{29}N_2O_2^+$: 461.2224; found: 461.2239.

Methyl 2-(1-Methyl-1*H*-Indol-3-yl)-*N*-Phenyl-2-(*p*-tolyl)acetimidate (6p)

Yield, obtained by following GP1: 100 mg (54%)

Orange oil; $R_f = 0.57$ (EtOAc–hexane, 1:5).

IR (film): 3052, 3021, 2952, 2869, 2854, 1737, 1662, 1595, 1511, 1461, 1375, 1330, 1247, 1153, 1023, 900, 740, 698 cm^{-1}.

^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.30 – 7.26 (m, 3H), 7.23 – 7.17 (m, 2H), 7.12 (d, J = 8.1 Hz, 2H), 7.10 – 7.04 (m, 3H), 7.00 (ddd, J = 8.1, 7.0, 1.0 Hz, 1H), 6.88 (s, 1H), 6.79 (dd, J = 8.4, 1.2 Hz, 2H), 5.32 (s, 1H), 3.85 (s, 3H), 3.76 (s, 3H), 2.32 (s, 3H).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 163.1, 148.6, 137.2, 137.0, 136.4, 129.1 (2C), 129.1 (2C), 128.4, 128.35 (2C), 127.1, 123.1, 121.7, 121.5 (2C), 119.4, 119.1, 113.3, 109.3, 53.8, 42.8, 32.9, 21.2.

MS (ESI): $m/z = 369$ $[M + H]^+$

HRMS (TOF ES$^+$): m/z $[M + H]^+$ calcd for $C_{25}H_{25}N_2O^+$: 369.1961; found: 369.1961.

Methyl 2-(1-Benzyl-1*H*-Indol-3-yl)-*N*-(4-Chlorophenyl)-2-(4-Methoxyphenyl)acetimidate (6q)

Yield, obtained by following GP1: 106 mg (43%).

Yield, obtained by following GP2: 89 mg (36%).

Yellowish oil; yield; $R_f = 0.53$ (EtOAc–hexane, 1:5).

IR (film): 3028, 2948, 2836, 1736, 1666, 1610, 1510, 1466, 1302, 1242, 1176, 1092, 1031, 908, 835, 739 cm^{-1}.

^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.32 – 7.23 (m, 5H), 7.22 (d, J = 8.6 Hz, 2H), 7.19 – 7.12 (m, 3H), 7.08 (d, J = 7.2 Hz, 2H), 7.02 (ddd, J = 7.9, 7.0, 0.9 Hz, 1H), 6.95 (s, 1H), 6.81 (d, J = 9.1 Hz, 2H), 6.71 (d, J = 8.6 Hz, 2H), 5.34 – 5.22 (m, 3H), 3.83 (s, 3H), 3.78 (s, 3H).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 163.1, 158.5, 147.2, 137.7, 136.8, 132.1, 129.5 (2C), 129.1 (2C), 128.8 (2C), 127.9, 127.6, 127.3, 126.7 (2C), 123.1, 121.95, 121.5 (2C), 119.7, 119.4, 114.2, 113.8 (2C), 109.9, 55.3, 53.7, 50.1, 42.6.

MS (ESI): $m/z = 495$ $[M + H]^+$

HRMS (TOF ES$^+$): m/z $[M + H]^+$ calcd for $C_{31}H_{28}ClN_2O_2^+$: 495.1834; found: 495.1817.

Methyl 2-(1-Benzyl-5-Methoxy-1*H*-Indol-3-yl)-(4-Chlorophenyl)-2-(*p*-tolyl)acetimidate (6r)

Yield, obtained by following GP1: 94 mg (37%)

Brownish oil; $R_f = 0.49$ (EtOAc–hexane, 1:5).

IR (film): 3027, 2992, 2941, 2919, 2833, 1661, 1590, 1511, 1487, 1452, 1398, 1355, 1241, 1213, 1175, 1094, 1028, 903, 869, 829, 796, 732, 704, 643 cm^{-1}.

^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.31 – 7.28 (m, 2H), 7.28 – 7.25 (m, 1H), 7.23 (d, J = 8.6 Hz, 2H), 7.14 – 7.05 (m, 7H), 6.95 (s, 1H), 6.80 (dd, J = 8.6, 2.5 Hz, 1H), 6.73 (d, J = 8.6 Hz, 2H), 6.65 (d, J = 2.5 Hz, 1H), 5.29 – 5.22 (m, 3H), 3.83 (s, 3H), 3.72 (s, 3H), 2.32 (s, 3H).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 163.7, 154.0, 147.3, 137.7, 136.7, 136.58, 131.9, 129.2 (2C), 129.1 (2C), 128.8 (2C), 128.6, 128.4, 128.3 (2C), 127.7, 127.7, 126.6 (2C), 122.9 (2C), 113.0, 112.3, 110.7, 101.0, 55.8, 53.9, 50.4, 42.9, 21.2.

MS (ESI): $m/z = 509$ $[M + H]^+$

HRMS (TOF ES$^+$): m/z $[M + H]^+$ calcd for $C_{32}H_{30}ClN_2O_2^+$: 509.1990; found: 509.1962.

1-Benzyl-3-(Methoxy(*p*-tolyl)Methyl)-1*H*-Indole (7)

According to GP1 without an isocyanide addition compound **7** (155 mg, 91%) was obtained as an orange oil; $R_f = 0.71$ (EtOAc–hexane, 1:5).

IR (film): 3029, 2922, 2816, 1717, 1613, 1550, 1511, 1495, 1466, 1453, 1355, 1335, 1306, 1249, 1174, 1084, 1028, 956, 810, 777, 740, 695, 639, 573 cm^{-1}.

^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.63 (d, J = 8.1 Hz, 1H), 7.37 (d, J = 8.1 Hz, 2H), 7.29 – 7.23 (m, 3H), 7.22 (d, J = 8.1 Hz, 1H), 7.18 – 7.12 (m, 3H), 7.09 – 7.05 (m, 3H), 6.88 (s, 1H), 5.56 (s, 1H), 5.28 – 5.20 (m, 2H), 3.42 (s, 3H), 2.34 (s, 3H).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 138.8, 137.6, 137.161, 129.1, 128.8, 127.6, 127.3, 127.2, 127.1, 126.7, 122.1, 120.2, 119.6, 117.2, 109.9, 79.6, 56.7, 50.1, 21.3.

MS (EI, 70 eV): m/z (%) = 341 (11) $[M]^+$, 310 (63) $[M - OCH_3]^+$, 250 (7), 218 (6), 204 (6), 91 $[C_7H_7]^+$ (100).

Synthesis of Amides 8

General Procedure

A salt **1** (0.5 mmol) and K_2CO_3 (100 mg, 0.75 mmol) were added to a solution of 0.65 mmol of isonitrile in a mixture of MeOH (1 mL), MeCN (1 mL) and H_2O (0.2 mL). The reaction mixture was stirred at room temperature for 12 h. It was then diluted with 40 ml of EtOAc, washed with H_2O (2 × 25 mL), brine (20 mL) and dried over anhydrous Na_2SO_4. The EtOAc was evaporated in vacuo. The residue was chromatographed on a column of silica gel with EtOAc–hexane.

N-Benzyl-2-(1-Benzyl-1*H*-Indol-3-yl)-2-(*p*-tolyl)acetamide (8a)

White solid; yield 132 mg (59%); mp 176–178°C; $R_f = 0.42$ (EtOAc–hexane, 1:3).

IR (film): 3299, 3087, 3029, 2949, 2920, 2874, 1645, 1612, 1532, 1496, 1433, 1356, 1334, 1222, 1030, 807, 768, 745, 696, 649 cm^{-1}.

^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.44 (d, J = 8.1 1H), 7.27 – 7.21 (m, 9H), 7.17 – 7.11 (m, 5H), 7.07 – 7.03 (m, 3H), 6.95 (d, J = 0.8 Hz, 1H), 6.12 (dd, J = 6.0, 5.7 Hz, 1H), 5.23 (s, 2H), 5.15 (s, 1H), 4.50 (dd, J = 15.1, 6.0 Hz, 1H), 4.41 (dd, J = 15.1, 5.7 Hz, 1H), 2.32 (s, 3H).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 172.5, 138.4, 137.5, 137.0, 136.9, 136.5, 129.5 (2C), 128.8 (2C), 128.7 (2C), 128.5 (2C), 127.9, 127.7 (2C), 127.7, 127.5, 127.4, 126.7 (2C), 122.4, 119.8, 119.5, 114.0, 110.1, 50.9, 50.2, 43.8, 21.2.

MS (ESI): $m/z = 445\ [M + H]^+$

HRMS (TOF ES^+): $m/z\ [M + H]^+$ calcd for $C_{31}H_{29}N_2O^+$: 445.2274; found: 445.2301.

N-Benzyl-2-(1-Benzyl-1*H*-Indol-3-yl)-2-(4-Methoxyphenyl)acetamide (8b)

White solid; yield 144 mg (63%); mp 177–179°C; $R_f = 0.41$ (EtOAc–hexane, 1:3).

IR (film): 3328, 3062, 3028, 2930, 2837, 1735, 1642, 1610, 1510, 1466, 1354, 1303, 1243, 1179, 1029, 734, 698 cm^{-1}.

^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.42 (d, J = 8.1, 1H), 7.28 (d, J = 8.6 Hz, 2H), 7.26 – 7.21 (m, 7H), 7.19 – 7.13 (m, 3H), 7.07 – 7.02 (m, 3H), 6.95 (s, 1H), 6.85 (d, J = 8.6 Hz, 2H), 6.12 (dd, J = 6.1, 5.6 Hz, 1H), 5.24 (s, 2H), 5.13 (s, 1H), 4.50 (dd, J = 14.9, 6.1 Hz, 1H), 4.42 (dd, J = 14.9, 5.6 Hz, 1H), 3.78 (s, 3H).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 172.6, 158.8, 138.4, 137.4, 137.0, 131.63, 129.7 (2C), 128.9 (2C), 128.7 (2C), 127.9, 127.7 (2C), 127.7, 127.4, 127.4, 126.7 (2C), 122.4, 119.8, 119.5, 114.2 (2C), 114.1, 110.1, 55.4, 50.5, 50.2, 43.8.

MS (ESI): $m/z = 461\ [M + H]^+$

HRMS (TOF ES^+): $m/z\ [M + H]^+$ calcd for $C_{31}H_{29}N_2O_2^+$: 461.2224; found: 461.2243.

N-Benzyl-2-(4-Methoxyphenyl)-2-(1-Methyl-1*H*-Indol-3-yl)acetamide (8c)

White solid; yield 101 mg (53%); mp 207–209°C; $R_f = 0.26$ (EtOAc–hexane, 1:3).

IR (film): 3280, 3088, 3006, 2920, 2835, 1647, 1607, 1557, 1507, 1473, 1419, 1342, 1248, 1223, 1174, 1031, 753 cm^{-1}.

^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.42 (d, J = 7.6, Hz, 1H), 7.30 – 7.20 (m, 7H), 7.18 –7.14 (m, 2H), 7.07 (ddd, J = 8.1, 7.0, 1.0 Hz, 1H), 6.86 (d, J = 9.1 Hz, 2H), 6.76 (s, 1H), 6.19 (dd, J = 6.1, 5.6 Hz, 1H), 5.12 (s, 1H), 4.51 (dd, J = 14.9, 6.1 Hz, 1H), 4.41 (dd, J = 14.9, 5.6 Hz, 1H), 3.79 (s, 3H), 3.70 (s, 3H)

^{13}C NMR (150 MHz, $CDCl_3$): δ = 173.0, 158.8, 138.3, 137.4, 131.6, 129.7 (2C), 128.7 (2C), 128.5, 127.8 (2C), 127.5, 127.1, 122.2, 119.5, 119.3, 114.2 (2C), 113.3, 109.5, 55.4, 50.3, 43.8, 32.9.

MS (ESI): $m/z = 385\ [M + H]^+$

HRMS (TOF ES^+): $m/z\ [M + H]^+$ calcd for $C_{25}H_{24}N_2O_2^+$: 385.1911; found: 385.1919.

N-Benzyl-2-(1-Methyl-1*H*-indol-3-yl)-2-Phenylacetamide (8d)

White solid; yield 88 mg (50%); mp 146–148°C; $R_f = 0.29$ (EtOAc–hexane, 1:3).

IR (film): 3256, 3050, 2940, 2098, 1736, 1634, 1542, 1475, 1451, 1372, 1335, 1216, 1152, 1111, 1029, 990, 745, 699, 584 cm^{-1}.

^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.44 (d, J = 8.1 Hz, 1H), 7.38 – 7.36 (m, 2H), 7.35 – 7.31 (m, 2H), 7.30 – 7.21 (m, 6H), 7.19 – 7.15 (m, 2H), 7.08 (ddd, J = 8.1, 7.0, 1.0 Hz, 1H), 6.77 (d, J = 1.0 Hz, 1H), 6.18 (dd, J = 6.1, 5.7 Hz, 1H), 5.16 (s, J = 6.8 Hz, 1H), 4.52 (dd, J = 15.5, 6.1 Hz, 1H), 4.42 (dd, J = 15.1, 5.7 Hz, 1H), 3.70 (s, 3H).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 172.4, 139.7, 138.4, 137.3, 128.8 (2C), 128.7 (2C), 128.6 (2C), 128.6, 127.8 (2C), 127.5, 127.2, 127.1, 122.2, 119.6, 119.3, 113.1, 109.5, 51.2, 43.8, 32.9.

MS (ESI): $m/z = 355\ [M + H]^+$

HRMS (TOF ES^+): $m/z\ [M + H]^+$ calcd for $C_{24}H_{23}N_2O^+$: 355.1805; found: 355.1808.

N-Benzyl-2-(1-Benzyl-5-Bromo-1*H*-Indol-3-yl)-2-(*p*-tolyl)acetamide (8e)

White solid; yield 132 mg (51%); mp 184–186°C; $R_f = 0.15$ (EtOAc–hexane, 1:5).

IR (film): 3250, 3068, 3029, 2923, 1645, 1560, 1511, 1469, 1356, 1234, 1173, 1021, 869, 817, 802, 733, 697 cm^{-1}.

^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.55 (d, J = 2.0 Hz, 1H), 7.30 – 7.25 (m, 8H), 7.22 (dd, J = 8.6, 2.0 Hz, 1H) 7.17 (d, J = 7.1 Hz, 2H), 7.13 (d, J = 8.0 Hz, 2H), 7.06 (d, J = 8.6 Hz, 1H), 7.01 (dd, J

= 7.6, 1.9 Hz, 2H), 7.00 (s, 1H), 6.07 – 6.02 (m, 1H), 5.21 (s, 2H), 5.05 (s, 1H), 4.52 – 4.43 (m, 2H), 2.32 (s, 3H).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 172.1, 138.2, 137.2, 137.0, 136.0, 135.6, 129.7 (2C), 129.2, 129.1, 128.9 (2C), 128.8 (2C), 128.4 (2C), 127.9, 127.7 (2C), 127.5, 126.6 (2C), 125.2, 122.0, 113.5, 113.2, 111.6, 50.6, 50.5, 43.9, 21.2.

MS (ESI): $m/z = 523$ $[M + H]^+$

HRMS (TOF ES^+): m/z $[M + H]^+$ calcd for $C_{32}H_{28}BrN_2O^+$: 523.1380; found: 523.1398.

N-Benzyl-2-(1-Benzyl-5-Methoxy-1*H*-Indol-3-yl)-2-(*p*-tolyl)acetamide (8f)

White solid; yield 135 mg (57%); mp 168–170°C; $R_f = 0.13$ (EtOAc–hexane, 1:5).

IR (film): 3283, 3031, 2923, 1649, 1622, 1489, 1453, 1352, 1228, 1171, 1032, 918, 822, 794, 742, 699 cm^{-1}.

^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.26 (d, *J* = 8.1 Hz, 2H), 7.25 – 7.21 (m, 6H), 7.16 (dd, *J* = 7.6, 2.0 Hz, 2H), 7.13 (d, *J* = 8.1 Hz, 2H), 7.09 (d, *J* = 8.6 Hz, 1H), 6.99 – 7.04 (m, 2H), 6.87 (s, 1H), 6.86 (d, *J* = 2.4 Hz, 1H), 6.80 (dd, *J* = 8.9, 2.4 Hz, 1H), 6.19 (dd, *J* = 6.1, 5.8 Hz, 1H), 5.19 (s, 2H), 5.11 (s, 1H), 4.51 (dd, *J* = 15.1, 6.1 Hz, 1H), 4.43 (dd, *J* = 15.1, 5.8 Hz, 1H), 3.72 (s, 3H), 2.33 (s, 3H).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 172.5, 154.3, 138.4, 137.5, 136.9, 136.5, 132.2, 129.5 (2C), 128.8 (2C), 128.7 (2C), 128.6, 128.5 (2C), 127.8, 127.7 (2C), 127.7, 127.4, 126.6 (2C), 113.5, 112.7, 111.0, 101.0, 55.9, 50.9, 50.4, 43.8, 21.2.

MS (ESI): $m/z = 475$ $[M + H]^+$

HRMS (TOF ES^+): m/z $[M + H]^+$ calcd for $C_{32}H_{31}N_2O_2^+$: 475.2380; found: 475.2399.

2-(1-Benzyl-1*H*-Indol-3-yl)-*N*,2-bis(4-Methoxyphenyl)acetamide (8g)

White solid; yield 105 mg (44%); mp 208–210°C; $R_f = 0.57$ (EtOAc–hexane, 1:3).

IR (film): 3287, 3255, 3196, 3134, 3058, 3024, 2962, 2835, 1655, 1606, 1546, 1509, 1469, 1410, 1346, 1303, 1251, 1171, 1031, 969, 833, 794, 746, 730, 700 cm^{-1}.

^{1}H NMR (600 MHz, DMSO-d_6): δ = 10.20 (s, 1H), 7.53 (d, *J* = 9.1 Hz, 2H), 7.44 (s, 1H), 7.43 – 7.34 (m, 4H), 7.32 – 7.27 (m, 2H), 7.25 – 7.21 (m, 1H), 7.18 (d, *J* = 7.1 Hz, 2H), 7.09 – 7.04 (m, 1H), 6.99 – 6.95 (m, 1H), 6.90 – 6.84 (m, 4H), 5.41 (s, 2H), 5.26 (s, 1H), 3.71 (s, 3H) 3.70 (s, 3H).

^{13}C NMR (150 MHz, DMSO-d_6): δ = 170.2, 158.1, 155.2, 138.4, 136.1, 132.4, 132.3, 129.3 (2C), 128.5 (2C), 127.4, 127.3, 127.1, 127.0 (2C), 121.4, 120.7 (2C), 118.84, 118.82, 113.9 (2C), 113.7, 113.6 (2C), 110.2, 55.2, 55.0, 49.0, 48.6.

MS (ESI): $m/z = 477$ $[M + H]^+$

HRMS (TOF ES^+): m/z $[M + H]^+$ calcd for $C_{31}H_{29}N_2O_3^+$: 477.2173; found: 477.2193.

2-(1-Benzyl-1*H*-Indol-3-yl)-*N*-(4-Chlorophenyl)-2-(4-Methoxyphenyl)acetamide (8h)

White solid; yield 132 mg (54%); mp 179–181°C; $R_f = 0.30$ (EtOAc–hexane, 1:4).

IR (film): 3282, 3061, 3030, 2928, 1658, 1593, 1510, 1493, 1467, 1397, 1299, 1248, 1173, 1093, 1030, 824, 786, 739, 697 cm^{-1}.

^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.65 (s, 1H), 7.44 (d, *J* = 8.0 Hz, 1H), 7.35 (d, *J* = 9.0 Hz, 2H), 7.34 – 7.25 (m, 6H), 7.20 (d, *J* = 8.6 Hz, 2H), 7.19 – 7.16 (m, 1H), 7.10 – 7.06 (m, 3H), 7.01 (s, 1H), 6.87 (d, *J* = 8.6 Hz, 2H), 5.27 (s, 2H), 5.21 (s, 1H), 3.78 (s, 3H).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 171.0, 159.0, 137.3, 137.1, 136.4, 131.1, 129.7 (2C), 129.4, 129.0 (2C), 128.9 (2C), 128.0, 127.8, 127.2, 126.8 (2C), 122.6, 121.2 (2C), 120.1, 119.3, 114.4 (2C), 113.6, 110.3, 55.4, 51.3, 50.3.

MS (ESI): $m/z = 481$ $[M + H]^+$

HRMS (TOF ES^+): m/z $[M + H]^+$ calcd for $C_{30}H_{25}ClN_2O_2^+$: 481.1677; found: 481.1683.

DATA AVAILABILITY

The raw data supporting the conclusions of this manuscript will be made available by the authors, without undue reservation, to any qualified researcher.

AUTHOR CONTRIBUTIONS

NG and HN were responsible for designing and performing the experiments. NG, HN, AG and AV discussed the evolution of the project and revised the manuscript together. LV and EV directed the project and wrote the publication.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fchem.2019.00345/full#supplementary-material

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Isocyanide Reactions Toward the Synthesis of 3-(Oxazol-5-yl)Quinoline-2-Carboxamides and 5-(2-Tosylquinolin-3-yl)Oxazole

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A palladium-catalyzed three-component reaction between 5-(2-chloroquinolin-3-yl) oxazoles, isocyanides, and water to yield 3-(oxazol-5-yl)quinoline-2-carboxamides is described. Interestingly, sulfonylation occurred when the same reaction was performed with toluenesulfonylmethyl isocyanide (TosMIC) as an isocyanide source. The reaction with 5-(2-chloroquinolin-3-yl)oxazoles and TosMIC in the presence of Cs_2CO_3 in DMSO afforded 5-(2-Tosylquinolin-3-yl)oxazoles. In basic media, TosMIC probably decomposed to generate Ts^- species, which were replaced with Cl^-. Tandem oxazole formation with subsequent sulfonylation of 2-chloroquinoline-3-carbaldehydes to form directly 5-(2-tosylquinolin-3-yl)oxazoles was also investigated.

Keywords: palladium acetate, carboxamidation, isocynides, sulfonylation, TosMIC

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INTRODUCTION

Quinolines are heterocyclic compounds exhibiting diverse and well-documented bioactivity and physical properties as well as existing as scaffolds in complex structures of natural products (Michael, 2002; Hranjec et al., 2017). Accordingly, quinoline synthesis, and functionalization has attracted much attention from synthetic organic chemists (Marco-Contelles et al., 2009; Shiri et al., 2011; Prajapati et al., 2014; Sharma et al., 2018; Nainwal et al., 2019).

However, isocyanides play an important role in synthesizing *N*-containing heterocycles and are particularly widely applied in Ugi and Passirini reactions (Domling and Ugi, 2000; Domling, 2006). Amides are especially valuable as precursors in synthesizing of bioactive and natural structures, in medicinal chemistry as well as protein synthesis (Bode, 2006; Rönn et al., 2008).

Many natural products such as urukthapelstatin A have been isolated from marine sources, these contains, several aminocarbonyl and oxazole functional groups with cytotoxic activity against human lung cancer (Yu et al., 2009). Similarly, venturamides A and B showed *in vitro* antimalarial activity (Linington et al., 2007; Davyt and Serra, 2010). Additionally, aerucyclamid C, a hexameric cyclopeptide, extremely active against *T. brucei rhodesiense,* which causes sleeping sickness, and exhibits lower activity against *P. falciparum,* the deadliest species of *Plasmodium,* which causes malaria (Davyt and Serra, 2010). Microcyclamide A is a cyclic hexapeptide with three five-membered heterocycles. It is isolated from cyanobacterium *M. aeruginosa,* and it has exhibited cytotoxic effects against P388 murine leukemia (Ishida et al., 2000; Davyt and Serra, 2010; Raveh et al., 2010) (**Figure 1**).

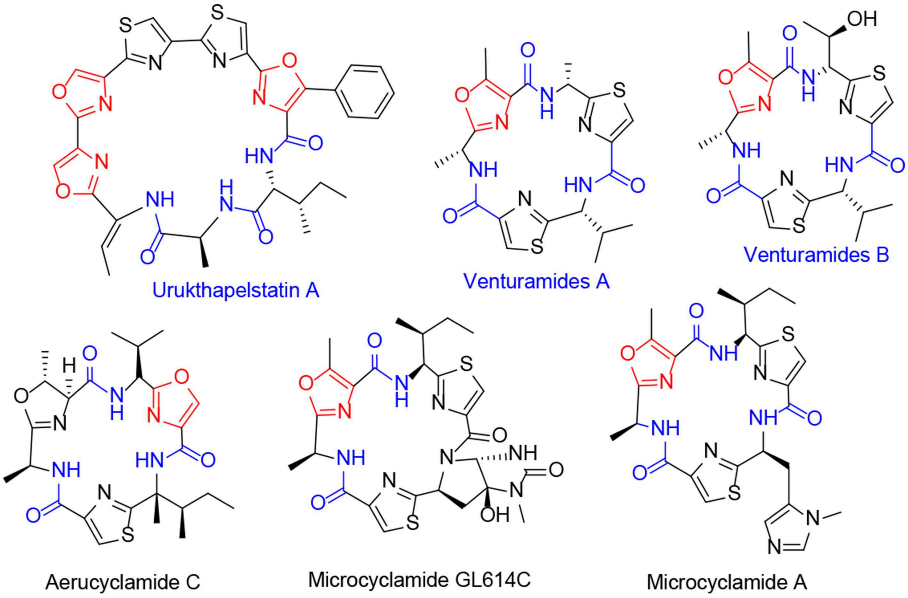


FIGURE 1 | Several natural products with amide and oxazole moieties.

Classical procedures for amide bond formation include reactions between carboxylic acids and amines (Linington et al., 2007; Davyt and Serra, 2010). Another route involves reactions of acyl halides, acyl azides, acyl imidazoles, anhydrides, or esters (activated carboxylic acid species) with amines (Ulijn et al., 2002; Montalbetti and Falque, 2005). As well as classical routes for amides synthesis which have own merits and demerits, direct aminocarbonylation from aryl halides in metal-catalyzed reactions has attracted attention from chemists due to its significant advantages benzamide preparation (Åkerbladh et al., 2017). In this regard, many synthetic methods have been introduced, including copper-catalyzed reactions of aryl halides and isocyanides in DMSO (Yavari et al., 2014). A palladium-catalyzed reaction was developed for amidation of aryl halides (Jiang et al., 2011), as well as the synthesis of 4-aminophthalazin-1(*2H*)-ones in a palladium-catalyzed reaction with isocyanide insertion in a multi-component reaction, which is difficult to achieve via a classical route (Vlaar et al., 2011). Palladium-catalyzed isocyanide insertion was applied to a carboxamidation/hydroamidation reaction to synthesize isoindolin-1-one derivatives (Pathare et al., 2016). Another example is the synthesis of isoquinolin-1(*2H*)-one derivatives via a palladium-catalyzed cascade reaction from isocyanide and amides (Wang et al., 2002; Tyagi et al., 2012; Chaudhary et al., 2013). Very recently, Guan et al reported an efficient method for the synthesis of multisubstituted 1*H*-imidazo-[4,5-*c*]quinoline derivatives via sequential van Leusen/Staudinger/aza-Wittig/carbodiimide-mediated cyclization (Guan et al., 2018).

MATERIALS AND METHODS

General

The solvents and chemicals purchased from Merck and Aldrich chemical companies. Unless otherwise mentioned they used without further purification. Melting points are taken on an Electrothermal 9100 apparatus and are uncorrected. IR spectras recorded on a Shimadzu Infra-Red Spectroscopy IR-435. Nuclear magnetic resonance (NMR) spectra recorded on a Bruker AVANCE Spectrometer (400 MHz for ^{1}H, 100 MHz for ^{13}C) in DMSO-d$_6$ and CDCl$_3$ as solvent, TMS used as internal standard. The elemental analysis carried out with a Leco CHNS model 932. Mass spectra recorded on Agilent Technology (HP) 5973 Network Mass Selective Detector operating at an ionization potential of 70 eV.

The Typical Procedure for the Synthesis of 5-(2-chloroquinolin-3-yl)oxazole 3a

A mixture of 2-chloro-quinoline-3-carbaldehyde **2a** (191 mg, 1.0 mmol), *p*-toluenesulfonylmethyl isocyanide **1** (234 mg, 1.2 mmol) and K$_2$CO$_3$ (341 mg, 2.5 equiv.) was added to EtOH (5.0 ml) and stirred for 3.5 h, at room temperature. After completion of the reaction, monitored by TLC, the mixture poured into cool water and stirred for 30 min. The product **3a** filtered, washed with water two times and dried on the air.

The Typical Procedure for the Synthesis of N-cyclohexyl-3-(oxazol-5-yl)quinoline-2-carboxamide 5a

A mixture of 5-(2-chloroquinolin-3-yl)oxazole **3a** (230 mg, 1.0 mmol), of Pd(OAc)$_2$ (11 mg, 5 mol%) and Cs$_2$CO$_3$ (325 mg, 1.0 mmol) stirred in DMSO:H_2O, 9:1 (5 mL) at 80°C for 15 min. Cyclohexyl isocyanide **4a** (120 mg, 1.1 mmol) was added and the reaction stirred for 4 h. After completion of the reaction (the progress of the reaction was monitored by TLC) organic layer was extracted by DCM, washed with brine, dried over Na_2SO_4 and its solvent evaporated on a rotary evaporator. The residue was washed with 2-propanol and recrystallized in methanol to give **5a**. It is noteworthy that **5a** and **5h** purified by washing with 2-propanol but other derivatives were purified by a column chromatography (*n*-hexan: ethyl acetate 3:1) and recrystallized in EtOH.

The Typical Procedure for the Synthesis of 5-(2-tosylquinolin-3-yl)oxazole 6a-e

A mixture of 2-chloro-quinoline-3-carbaldehyde **2a** (191 mg, 1.0 mmol), *p*-toluenesulfonylmethyl isocyanide **1** (468 mg, 2.4 mmol) and Cs_2CO_3 (810 mg, equiv.) was added to DMSO (5.0 ml) and stirred for 5 h at 80°C. After completion of the reaction and monitored by TLC, the mixture poured into cool water and stirred for 30 min, then extracted with DCM. The product **6a** purified by a column chromatography (*n*-hexan: ethyl acetate 4:1).

Supplementary Material

N-Cyclohexyl-3-(oxazol-5-yl) quinolone-2-carboxamide (5a)

Copies of NMR spectra are provided as **Supplementary Materials**. White powder, mp.: 123–128°C. **^{1}H-NMR** (400 MHz, $CDCl_3$): δ = 1.25–1.52 (m, 5H), 1.68–171 (m, 1H), 1.80–1.85 (m, 2H), 2.10–213 (m, 2H), 3.99–4.02 (m, 1H), 7.60 (s, 1H), 7.67 (t, *J* = 8.0 Hz, 2H), 7.82 (t, *J* = 7.8 Hz, 1H), 7.90 (d, *J* = 8.4 Hz, 1H), 8.03 (s, 1H), 8.14 (d, *J* = 8.4 Hz, 1H), 8.44 (s, 1H) ppm. **^{13}C-NMR** (100 MHz, $CDCl_3$): δ = 25.0, 25.6, 33.0, 48.6, 120.4, 125.9, 127.9, 128.0, 128.6, 129.5 131.0, 137.9, 145.9, 148.5, 148.8, 151.0, 164.3 ppm. **Mass**: m/z 321 (M+) (calcd. For $C_{19}H_{19}N_3O_2$: 321.37). FT-IR (KBr): ν_{max}: 1604, 3444 cm^{-1}. **Anal. calcd. for** $C_{19}H_{19}N_3O_2$: C, 71.01; H, 5.96; N, 13.08. Found: C,71.10; H,5.81; N,13.17.

N-Cyclohexyl-8-methyl-3-(oxazol-5-yl)quinolone-2-carboxamide (5b)

White powder, mp: 181–185°C. **^{1}H-NMR** (400 MHz, DMSO-d_6): δ = 1.15–1.74 (m, 10H), 2.75 (s, 3H), 3.83 (m, 1H), 7.52 (s, 1H), 7.63 (d, *J* = 8.0 Hz, 1H), 7.73 (d, *J* = 6.8 Hz, 1H), 7.97 (d, *J* = 8.0 Hz, 1H), 8.60 (s, 1H), 8.74 (s, 1H) ppm. **^{13}C-NMR** (100 MHz, DMSO-d_6): δ = 17.8, 25.0, 25.6, 25.8, 32.5, 33.8, 48.5, 118.6, 121.8, 125.0, 126.7, 127.6, 128.3, 131.4, 135.2, 136.9, 145.0, 147.8, 153.0, 167.0 ppm. **Mass**: m/z 335 (M^+) (calcd. for $C_{20}H_{21}N_3O_2$: 335.40). FT-IR (KBr): ν_{max}: 1646, 2853, 2922, 3310, 3444 cm^{-1}. Anal. calcd. for $C_{20}H_{21}N_3O_2$: C, 71.62; H, 6.31; N, 12.53%. Found: C, 71.55; H, 6.47; N, 12.42%.

N-Butyl-6-methyl-3-(oxazol-5-yl)quinoline-2-carboxamide (5c)

White powder, mp: 124–127°C. **^{1}H-NMR** (400 MHz, $CDCl_3$): δ = 1.01 (t, *J* = 7.2 Hz, 3H), 1.45–1.54 (m, 2H), 1.67–1.74 (m, 2H), 2.61 (s, 3H), 3.53 (dd, *J* =13.4 Hz, *J* = 6.8 Hz, 2H), 7.60 (s, 1H), 7.65 (s, 1H), 7.68 (s, 1H), 7.77 (s, 1H), 8.03 (t, *J* = 5.2 Hz, 2H), 8.37 (s, 1H) ppm. **^{13}C-NMR** (100 MHz, $CDCl_3$): δ = 13.8, 20.2, 21.8, 31.7, 39.5, 120.4, 125.7, 125.8, 126.5, 126.6, 128.1, 129.0, 133.4, 137.2, 138.9, 142.9, 150.9, 165.2 ppm. **Mass**: m/z 309 (M^+) (calcd for $C_{18}H_{19}N_3O_2$: 309.36). FT-IR (KBr): ν_{max}: 1542, 1652, 2858, 2928, 2956, 2922, 3114, 3299 cm^{-1}. **Anal. calcd. for**: $C_{18}H_{19}N_3O_2$, C, 69.88; H, 6.19; N, 13.58%. Found C, 67.03; H, 6.24; N, 13.65%.

N-Cyclohexyl-6-methoxy-3-(oxazol-5-yl)quinoline-2-carboxamide (5d)

White powder, mp: 157–162°C. **^{1}H-NMR** (400 MHz,DMSO-d_6): δ = 1.04–1.27 (m, 5H), 1.57–1.74 (m, 5H), 3.93(s, 3H), 3.93 (m, 1H), 7.52 (dd, *J* = 9.2, *J* = 2.8 Hz, 1H), 7.61 (d, *J* = 2.8 Hz, 1H), 7.92 (d, *J* = 9.2 Hz, 1H), 7.96 (s, 1H), 8.71 (s, 1H), 8.77 (s,1H) ppm. **^{13}C-NMR** (100 MHz, DMSO-d_6): δ = 24.9, 25.8, 30.8, 31.2, 33.8, 47.9, 56.2, 106.7, 115.8, 121.3, 124.6, 127.5, 128.3, 129.6, 135.9, 142.4, 143.1, 146.5, 153.4, 158.7 ppm. **Mass**: m/z 351 (M+) (calcd. for $C_{20}H_{21}N_3O_3$:351.40). **FT-IR** (KBr): ν_{max}: 1666, 2927, 2966, 3286, 3423 cm^{-1}. **Anal. calcd. for** $C_{20}H_{21}N_3O_3$: C, 68.36; H, 6.02; N, 11.96%. Found: C, 68.47; H, 6.14; N, 12.11%.

N-Cyclohexyl-3-(oxazol-5-yl)benzo[h]quinoline-2-carboxamide (5e)

White powder, mp: 224–267°C. **^{1}H-NMR** (400 MHz, $CDCl_3$): δ = 1.28–1.58 (m, 6H), 1.85–1.88 (m, 2H), 2.16–2.19 (m, 2H), 4.07-4.10 (m, 1H), 7.30 (s, 1H), 7.74 (d, *J* = 2.4 Hz, 1H), 7.79-7.85 (m, 3H), 7.93 (d, *J* = 8.8 Hz, 1H), 7.97 (d, *J* = 7.6 Hz, 1H), 8.07 (s, 1H), 8.49 (s, 1H), 9.19 (d, *J* = 7.6 Hz, 1H) ppm. **^{13}C-NMR** (100 MHz, $CDCl_3$): δ = 24.9, 25.7, 29.7, 33.2, 48.5, 77.2, 121.3, 124.3, 124.7, 126.6, 126.9, 127.7, 128.2, 129.1, 130.1, 130.6, 134.1, 137.5, 144.2, 146.7, 148.5, 151.1, 164.5 ppm. **Mass**: m/z 371 (M^+) (calcd for $C_{23}H_{21}N_3O_2$:371.43). **FT-IR** (KBr): ν_{max}: 1646, 2852, 2936, 3119, 3294, 3448 cm^{-1}. **Anal. calcd. for**: $C_{23}H_{21}N_3O_2$, C, 74.37; H, 5.70; N, 11.31%. Found: C, 74.29; H, 5.84; N, 11.52%.

6-Chloro-N-cyclohexyl-3-(oxazol-5-yl)quinoline-2-carboxamide (5f)

White powder, mp: 226–232°C. **^{1}H-NMR** (400 MHz, $CDCl_3$): δ = 1.25–1.52 (m, 5H), 1.68–1.83 (m, 3H), 2.09–2.12 (m, 2H), 3.94–4.04 (m, 1H), 7.54 (d, *J* = 8.0 Hz, 1H), 7.63 (s, 1H), 7.71 (dd, *J* = 9.0 Hz, *J* = 2.4 Hz, 1H), 7.86 (d, *J* = 2.4 Hz, 1H), 8.02 (s, 1H), 8.05 (d, *J* = 9.2 Hz, 1H), 8.34 (s, 1H) ppm. **^{13}C-NMR** (100 MHz, $CDCl_3$): δ = 24.9, 25.6, 33.0, 48.7, 77.3, 121.2, 126.4, 126.6, 128.5, 131.0, 131.9, 134.5, 136.3, 144.1, 147.9, 149.0, 151.2, 164.2 ppm. **Mass**: m/z 355 (M+) (calcd. for $C_{19}H_{18}$ ClN_3O_2: 355.82). **FT-IR** (KBr): ν_{max}: 663, 1649, 2852, 2923, 3279, 3443 cm^{-1}. Anal. calcd. for: $C_{19}H_{18}ClN_3O_2$, C, 64.13; H, 5.10; N, 11.81%. Found: C, 64.20; H, 5.16; N, 11.70%.

N-(tert-Butyl)-6-chloro-3-(oxazol-5-yl)quinoline-2-carboxamide (5g)

White powder, mp: 190–197°C. **^{1}H-NMR** (400 MHz, DMSO-d_6): δ = 1.43 (s, 9H), 7.75 (s, 1H), 7.86 (dd, *J* = 9.2 Hz, *J* = 2.4 Hz, 1H), 8.14 (d, *J* = 8.8 Hz, 1H), 8.28 (d, *J* = 2.4 Hz, 1H), 8.46 (s, 1H), 8.64

(s, 1H), 8.76 (s, 1H) ppm. **^{13}C-NMR** (100 MHz, DMSO-d$_6$): δ = 28.8, 51.5, 119.5, 125.5, 127.4, 128.3, 131.3, 131.8, 132.7, 133.8, 144.5, 147.4, 153.4, 167.1 ppm. **Mass**: m/z 329.78 (M+) (calcd. for $C_{17}H_{16}N_3O_2$: 329.09). FT-IR (KBr): ν_{max}: 1626, 2852, 2928, 3334, 3423 cm^{-1}. Anal. calcd. for $C_{17}H_{16}$ ClN_3O_2: C, 61.91; H, 4.89; N, 12.74. Found: C, 62.04; H, 4.95; N, 12.89.

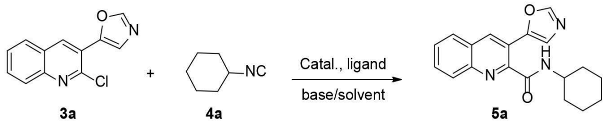
N-(tert-Butyl)-3-(oxazol-5-yl)quinolone-2-carboxamide (5h)

White powder, mp: 102–106°C. **^{1}H-NMR** (400 MHz, DMSO-d$_6$): δ = 1.43 (s, 9H), 7.56 (s, 1H), 7.72 (t, J =7.4 Hz, 1H), 7.87 (t, J =7.6 Hz, 1H), 8.13 (t, J = 8.8 Hz, 2H), 8.41 (s, 1H), 8.61(s, 1H), 8.77 (s, 1H) ppm. **^{13}C-NMR** (100 MHz, DMSO-d$_6$): δ = 28.8, 51.4, 118.7, 125.1, 127.5, 128.4, 128.8, 129.1, 131.4, 134.7, 146.0, 147.8, 153.0, 153.1, 167.4 ppm. **Mass**: m/z 295 (M+) (calcd. for $C_{17}H_{17}N_3O_2$: 295.34). **FT-IR** (KBr): ν_{max}: 1658, 2904, 2966, 3422 cm^{-1}. **Anal. calcd. for** $C_{17}H_{17}N_3O_2$: C, 69.14; H, 5.80; N, 14.23%. Found: C, 69.20; H, 5.87; N, 14.35%.

5-(2-Tosylquinolin-3-yl)oxazole (6a)

White powder, mp: 149–152°C. ^{1}H-NMR (400 MHz, DMSO-d$_6$): δ = 2.46 (s, 3H), 7.50 (d, J = 7.2 Hz, 2H), 7.77–7.90 (m, 6H), 8.18 (d, J = 7.6 Hz, 1H), 8.69 (s, 1H), 8.92 (s, 1H) ppm. ^{13}C-NMR (100 MHz, DMSO-d$_6$): δ = 21.6, 118.2, 127.6, 128.2, 128.9, 129.5, 129.6, 130.1, 130.6, 132.9, 135.5, 141.1, 144.9, 145.3, 145.6, 153.4, 155.1 ppm. Mass: m/z 350 (M$^+$) (calcd for $C_{19}H_{14}N_2O_3S$:350.39). FT-IR (KBr): ν_{max}: 683, 1073, 1103, 2851, 2920 cm^{-1}. Anal. calcd. for: $C_{19}H_{14}N_2O_3S$, C, 65.13; H, 4.03; N, 7.99; S, 9.15%. Found: C, 65.23; H, 4.14; N, 8.06; S, 9.21%.

TABLE 1 | Optimization of the reaction condition for the synthesis of *N*-cyclohexyl-3-(oxazol-5-yl)quinoline-2-carboxamide **5a** from **3a**.



Entry	Solvent	Base	Catalyst/Ligand	Time(h)	Yield 5a[a] (%)
1	Dioxane	Cs_2CO_3	$Pd(OAc)_2/PPh_3$	8	86
2[c]	CH_3CN	Cs_2CO_3	$Pd(OAc)_2/PPh_3$	8	21
3[c]	EtOH	Cs_2CO_3	$Pd(OAc)_2/PPh_3$	8	0
4	Toluene	Cs_2CO_3	$Pd(OAc)_2/PPh_3$	8	5
5	DMF	Cs_2CO_3	$Pd(OAc)_2/PPh_3$	8	82
6	DMSO	Cs_2CO_3	$Pd(OAc)_2/PPh_3$	6	92
7	DMSO	Cs_2CO_3	$Pd(OAc)_2$/-	1.5	92
8	DMSO	Cs_2CO_3	$PdCl_2$	12	74
9	DMSO	Cs_2CO_3	$Pd(PPh_3)_3$	12	61
10	DMSO	Cs_2CO_3	–	12	0
11	DMSO	K_2CO_3	$Pd(OAc)_2$/–	12	90
12	DMSO	NaOAc	$Pd(OAc)_2$/–	12	20
13	DMSO	KO^{t}Bu	$Pd(OAc)_2$/–	12	48
14	DMSO	DABCO	$Pd(OAc)_2$/–	12	5
15	DMSO	Et_3N	$Pd(OAc)_2$/–	12	0

[a]*Isolated yields.* [b]*All reactions were carried out using* ***3a*** *(1 mmol),* ***4a*** *(1.1 mmol), catalyst (5 mol %), base (1 mmol), and solvent (2.0 mL) and 80°C unless otherwise noted.* [c]*At reflux.*

5-(8-Methyl-2-tosylquinolin-3-yl)oxazole (6b)

White powder, mp: 162–167°C. ^{1}H-NMR (400 MHz, DMSO-d$_6$): δ = 2.18 (s, 3H), 2.50 (s, 3H), 7.55 (d, J = 8.0 Hz, 1H), 7.71 (d, J = 6.8 Hz, 2H), 7.88 (s, 1H), 7.90 (d, J = 7.6 Hz, 2H), 8.03 (dd, J = 6.8 Hz, J = 2.8 Hz, 1H), 8.73 (s, 1H), 8.95 (s, 1H) ppm. ^{13}C-NMR (100 MHz, DMSO-d$_6$): δ = 16.5, 21.7, 117.5, 126.6, 127.7, 128.3, 129.9, 130.1, 130.4, 132.5, 135.3, 137.4, 140.3, 143.5, 145.3, 145.5, 153.6, 153.8 ppm. Mass: m/z 364 (M$^+$) (calcd for $C_{20}H_{16}N_2O_3S$:364.42). FT-IR (KBr): ν_{max}: 1294, 1379, 2852, 2922 cm^{-1}. Anal. calcd. for: $C_{20}H_{16}N_2O_3S$, C, 65.92; H, 4.43; N, 7.69; S, 8.80%. Found: C, 66.03; H, 4.49; N, 7.78; S, 8.93%.

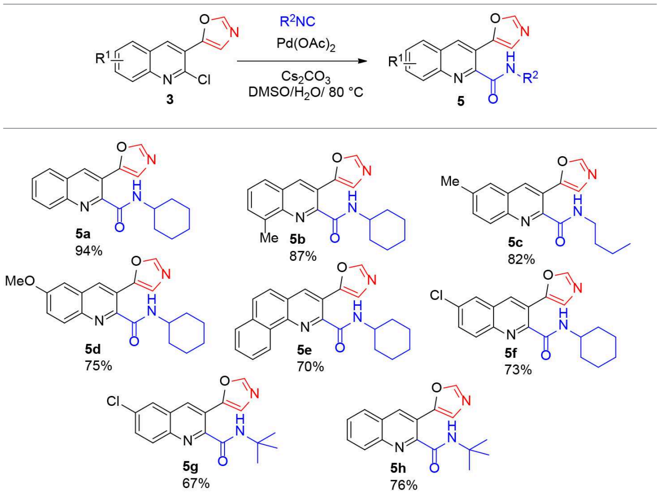
5-(6-Methyl-2-tosylquinolin-3-yl)oxazole (6c)

White powder, mp: 124–127°C. ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 2.51 (s, 3H), 2.59 (s, 3H), 7.30 (s, 1H), 7.38 (d, J = 6.4 Hz, 2H), 7.62 (d, J = 8.4 Hz, 1H), 7.68 (s, 1H), 7.84 (d, J = 8.0 Hz, 1H), 7.89 (d, J = 7.6 Hz, 2H), 8.10 (s, 1H), 8.44 (s, 1H) ppm. ^{13}C-NMR (100 MHz, DMSO-d$_6$): δ = 21.6, 21.7, 118.3, 127.3, 127.5, 128.2, 129.2, 129.5, 130.0, 135.1, 135.7, 140.2, 140.8, 142.9, 143.6, 145.2, 145.7, 153.3 ppm. Mass: m/z 364 (M$^+$) (calcd for $C_{20}H_{16}N_2O_3S$:364.42). FT-IR (KBr): ν_{max}: 823, 1375, 2853, 2923 cm^{-1}. Anal. calcd. for: $C_{20}H_{16}N_2O_3S$, C, 65.92; H, 4.43; N, 7.69; S, 8.80%. Found: C, 65.98; H, 4.49; N, 7.77; S, 8.86%.

5-(6-Methoxy-2-tosylquinolin-3-yl)oxazole (6d)

White powder, mp: 187–190°C. ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 2.51 (s, 3H), 3.99 (s, 3H), 7.16 (d, J = 8.8 Hz, 2H), 7.30

TABLE 2 | Synthesis of various derivatives of **5a**-**5h**[a].



[a]*All reactions were performed using* ***3*** *(1 mmol),* ***4*** *(1.1 mmol), $Pd(OAc)_2$ (5 mol%), Cs_2CO_3 (1 mmol), and 0.5 mL of H_2O in 4.5 mL of DMSO and 80°C.*

(s, 1H), 7.39 (s, 1H), 7.58 (d, *J* = 8.8 Hz, 2H), 7.84 (d, *J* = 9.2 Hz, 2H), 7.90 (d, *J* = 8.4 Hz, 1H), 8.10 (s, 1H), 8.42 (s, 1H) ppm. ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 37.1, 55.8, 104.6, 119.1, 124.0, 124.4, 124.8, 129.2, 129.6, 131.6, 135.6, 137.5, 138.4, 138.5, 144.5, 147.1, 147.6, 147.7 ppm. Mass: m/z 380 (M^+) (calcd for $C_{20}H_{16}N_2O_4S$: 380.42). FT-IR (KBr): ν_{max}: 1037, 117, 2850, 2920 cm^{-1}. Anal. calcd. for: $C_{20}H_{16}N_2O_4S$, C, 63.14; H, 4.24; N, 7.36; S, 8.43%. Found: C, 63.21; H, 4.29; N, 7.43; S, 8.55%.

5-(2-Tosylbenzo[h]quinolin-3-yl)oxazole (6e)

White powder, mp: 202–207°C. ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 2.60 (s, 3H), 7.30 (s, 1H), 7.52 (d, *J* = 8.0 Hz, 2H), 7.57 (t, *J* = 7.2 Hz, 1H), 7.70 (t, *J* = 6.8 Hz, 1H), 7.73 (d, *J* = 8.8 Hz, 1H), 7.89 (d, *J* = 8.4 Hz, 1H), 7.92 (d, *J* = 9.2 Hz, 1H), 8.04 (d, *J* = 8.4 Hz, 2H), 8.16 (d, *J* = 5.6 Hz, 1H), 8.20 (d, *J* = 8.4 Hz, 1H), 8.60 (s, 1H) ppm. ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 21.8, 119.0, 124.1, 124.4, 127.0, 127.8, 128.0, 128.7, 129.3, 129.3, 130.2, 130.5, 131.1, 134.0, 135.3, 137.5, 134.3, 144.8, 145.5, 151.6, 153.3 ppm. Mass: m/z 400 (M^+) (calcd for $C_{23}H_{16}N_2O_3S$: 400.45). FT-IR (KBr): ν_{max}: 1313, 1400, 2853, 2920 cm^{-1}. Anal. calcd. for: $C_{23}H_{16}N_2O_3S$, C, 68.98; H, 4.03; N, 7.00; S, 8.01%. Found: 69.06; H, 4.11; N, 7.12; S, 8.14%.

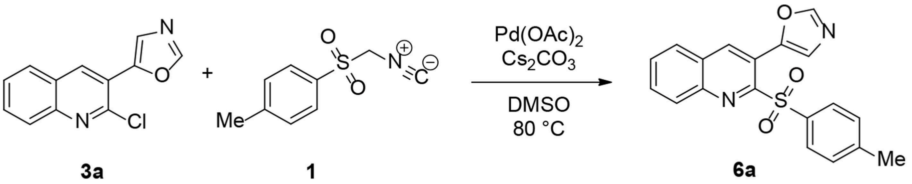
RESULTS AND DISCUSSION

In continuation of our interest in quinoline chemistry (Shiri et al., 2012, 2016a, 2017a) and isocyanide reactions (Shiri et al., 2016b, 2017b; Salehi and Shiri, 2019), we began our investigation with 2-chloroquinoline-3-carbaldehyde (**1**) and its two step reaction with two different isocyanides. In the presence of K_2CO_3, 2-chloroquinoline-3-carbaldehyde (**1**) and 4-toluenesulfonylmethyl isocyanide (TosMIC) (**2**) furnished 5-(2-chloroquinolin-3-yl)oxazole (**3a**). Several 5-(2-chloroquinolin-3-yl)oxazoles (**3**) were prepared under the same conditions. The reaction of quinoline **3a** with cyclohexyl isocyanide **4a** was selected as a model reaction in the presence of $Pd(OAc)_2$, Ph_3P, and Cs_2CO_3, in 1,4-dioxane with a few drops of H_2O as solvent at 80 °C. Desired product **5a** was obtained in 86% yield (**Table 1**). Solvent screening showed that DMSO is the best solvent (**Table 1**, entry 6). Other Pd sources such as $Pd(PPh_3)_4$ and $PdCl_2$ did not improve the product yield, however, the best yield was obtained with 5 mol% of $Pd(OAc)_2$ even without PPh_3 (**Table 1**, entries 7–9). Without palladium, the reaction did not occur (**Table 1**, entry 10). Moreover, the effect of base is crucial for reaction completion. Hence, different bases were investigated, including K_2CO_3, NaOAc, $(CH_3)_3OK$, DABCO, and Et_3N (**Table 1**, entries 14–18). In this survey, it was found that increasing the temperatures or the reaction time decreased the product yield.

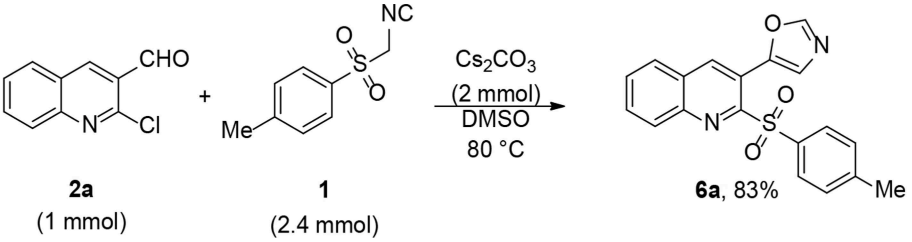
With the optimized reaction conditions in hand ($Pd(OAc)_2$ (5 mol%), Cs_2CO_3 (1 equiv.), DMSO + H_2O (9:1), 80°C), the generality of the reaction was explored (**Table 2**). A range of quinolines **3** bearing electron-donating groups, such as Me, and OMe and electron-withdrawing groups, such as Cl and benzo, reacted with cyclohexyl isocyanide and *n*-butylisocyanide to afford the corresponding 3-(oxazol-5-yl)quinoline-2-carboxamides **5a-f** in 70%-94% yields (**Table 2**). Moreover, the bulky *tert*-butyl isocyanide smoothly participated in this reaction to furnish **5g** and **5h** in 67 and 76% yield, respectively. The yield with 1,1,3,3-tetramethylbutyl isocyanide was too low to allow its isolation and characterization.

The scope of the reaction was explored using tosylmethyl isocyanide (TosMIC) **1** as another isocyanide source. Surprisingly, the reaction of **3a** with TosMIC under the optimized conditions afforded 5-(2-tosylquinolin-3-yl)oxazole (**6a**) (**Scheme 1**).

Although the reaction proceeded well without a palladium source, the presence of base is crucial. Among the bases Cs_2CO_3, K_2CO_3, NaOAc, *t*-BuOK, and DABCO, Cs_2CO_3 gave the best results.



SCHEME 1 | The reaction of TosMIC with **3a**.



SCHEME 2 | One-pot synthesis of 5-(6-methyl-2-tosylquinolin-3-yl)oxazole **6a**.

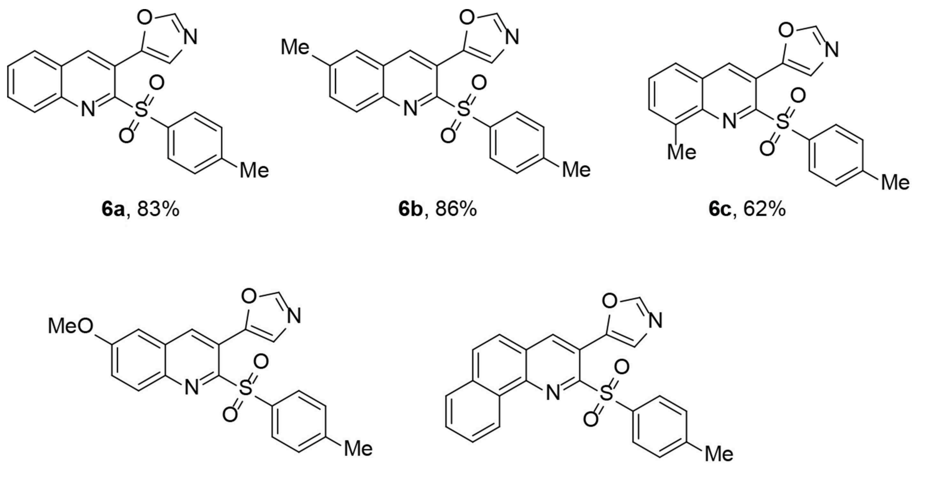


FIGURE 2 | 5-(2-Tosylquinolin-3-yl)oxazole **6**.

Encouraged by the tosylation results with TosMIC, we explored extending the reaction to tandem oxazole formation as well as tosylation of 2-chloroquinoline-3-carbaldehyde. Subjecting 2-chloroquinoline-3-carbaldehyde and TosMIC to the standard reaction conditions yielded 5-(2-tosylquinolin-3-yl)oxazole (**6a**) in 83% yield after 8 h (**Scheme 2**). Notably, sulfones are present in different bioactive compounds (Metzner and Thuillier, 1994; Fang et al., 2016); however, well-known sulfonylating agents include sulfonyl halides (Tocco et al., 2013; Zhang et al., 2015), sulfonyl hydrazides (Yuan et al., 2018; Zhang et al., 2018), and sodium sulfinate (Sun et al., 2017; Smith et al., 2018). A few studies used TosMIC as a sulfonyl precursor (Liu et al., 2014; Phanindrudu et al., 2016; Kadari et al., 2017). Furthermore, Bounar et al. reacted tosylmethyl isocyanide (TosMIC) with propargylic alcohols in the presence of silver acetate to efficiently yield (*E*)-vinyl sulfones (Bounar et al., 2015); this is the only study in which TosMIC plays a dual role as both an amide and a sulfonyl source.

The above cascade oxazole formation and sulfonylation strategy could be extended to other 2-chloroquinoline-3-carbaldehyde derivatives (**Figure 2**). A methyl group was tolerated on positions 6 and 8 of **2** to afford **6b** and **6c**, respectively, in 82 and 62% yields. Furthermore, quinoline **2d** reacted with TosMIC, affording **6d** in good yield. Product **6e**, existing an alternative decoration of the quinoline ring, was obtained in 85% yield.

Our proposed mechanism for the tosylation of quinoline involved *in situ* Ts^- generation by decomposition of *p*-toluenesulfonylmethyl-isocyanide **1** in the presence of base with subsequent aromatic nucleophilic substitution to form 2-sulfonyl quinoline **6**. Although application of TosMIC as a sulfonyl source was reported by Liu et al. for synthesizing sulfonyl benzoheteroles, the sulfonation mechanism involved aliphatic nucleophilic substitution (Liu et al., 2014).

CONCLUSION

In summary, we have developed a synthesis of 5-(2-chloroquinolin-3-yl)oxazole via a van Leusen procedure from 2-chloroquinoline-3-carbaldehydes and TosMIC, which were efficiently subjected to Pd-catalyzed amidation with isocyanides to form 3-(oxazol-5-yl)quinoline-2-carboxamides. The synthesis of 5-(2-tosylquinolin-3-yl)oxazole via a Cs_2CO_3-mediated domino process starting from 2-chloroquinoline-3-carbaldehydes with TosMIC was also demonstrated.

AUTHOR CONTRIBUTIONS

ZM, ZT, and SF synthesized all of the compounds with the help of ZY. MS supervised this work and wrote the paper with the help of ZY.

ACKNOWLEDGMENTS

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fchem.2019.00433/full#supplementary-material

Supplementary Data Sheet 1 | Isocyanide reactions toward the synthesis of 3-(Oxazol-5-yl)quinoline-2-carboxamides and 5-(2-Tosylquinolin-3-yl)oxazole.

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Multicomponent Reactions Upon the Known Drug Trimethoprim as a Source of Novel Antimicrobial Agents

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Novel antibiotic compounds have been prepared through a selective multicomponent reaction upon the known drug Trimethoprim. The Groebke-Blackburn-Bienaymé reaction involving this α-aminoazine, with a range of aldehydes and isocyanides afforded the desired adducts in one-step. The analogs display meaningful structural features of the initial drug together with relevant modifications at several points, keeping antibiotic potency and showing satisfactory antimicrobial profile (good activity levels and reduced growth rates), especially against methicillin-resistant *Staphylococcus aureus*. The new products may open new possibilities to fight bacterial infections.

Keywords: antibiotics, drugs, isocyanides, multicomponent reactions, resistant bacteria

INTRODUCTION

Trimethoprim (TMP, **1**, **Figure 1A**) is a well-known antibiotic, present in the *Model List of Essential Medicines* from the World Health Organization. TMP is usually used in combinationwith Sulfamethoxazole (SMX) to treat lower urinary tract infections and acute invasive diarrhea/bacterial dysentery as first and second choice, respectively (WHO, 2017), respiratory infections in cystic fibrosis patients caused by *Staphylococcus aureus*, among other many infections. Lately, it has also been used for preventing infections from the opportunistic pathogen *Pneumocystis carinii* (Urbancic et al., 2018), which normally causes pneumonia in patients with AIDS. Both drugs act on the folic acid biosynthetic route by inhibiting two enzymes: dihydrofolate reductase (DHFR) and dihydropteroate synthetase, respectively. Folate needs to be synthesized by bacteria and it is crucial in the biosynthetic pathway of thymidine, essential in DNA synthesis. Hence, when used in combination, these antibiotics display a synergistic effect in inhibiting bacterial growth and leading to eventual cell death (**Figure 1B**) (Torok et al., 2009; Katzung et al., 2012).

The combination of sulfonamides and DHFR inhibitors has been clinically used since 1968 when it was first approved in the UK (Cody et al., 2008; Torok et al., 2009). Unfortunately, resistance emerged soon and has become widespread (Huovinen et al., 1995; Ventola, 2015). Nowadays, antibiotic resistance is one of the world's most pressing public health problems with high morbidity and mortality rates (Centers for Disease Control and Prevention, 2017). Furthermore, finding active drugs to fight both multidrug resistant infections and organisms is becoming extremely challenging, as is often the case of methicillin-resistant *Staphylococcus aureus* (MRSA) and multidrug resistant *Pseudomonas aeruginosa*. In this context, the co-therapy with TMP and SMX turns out to be

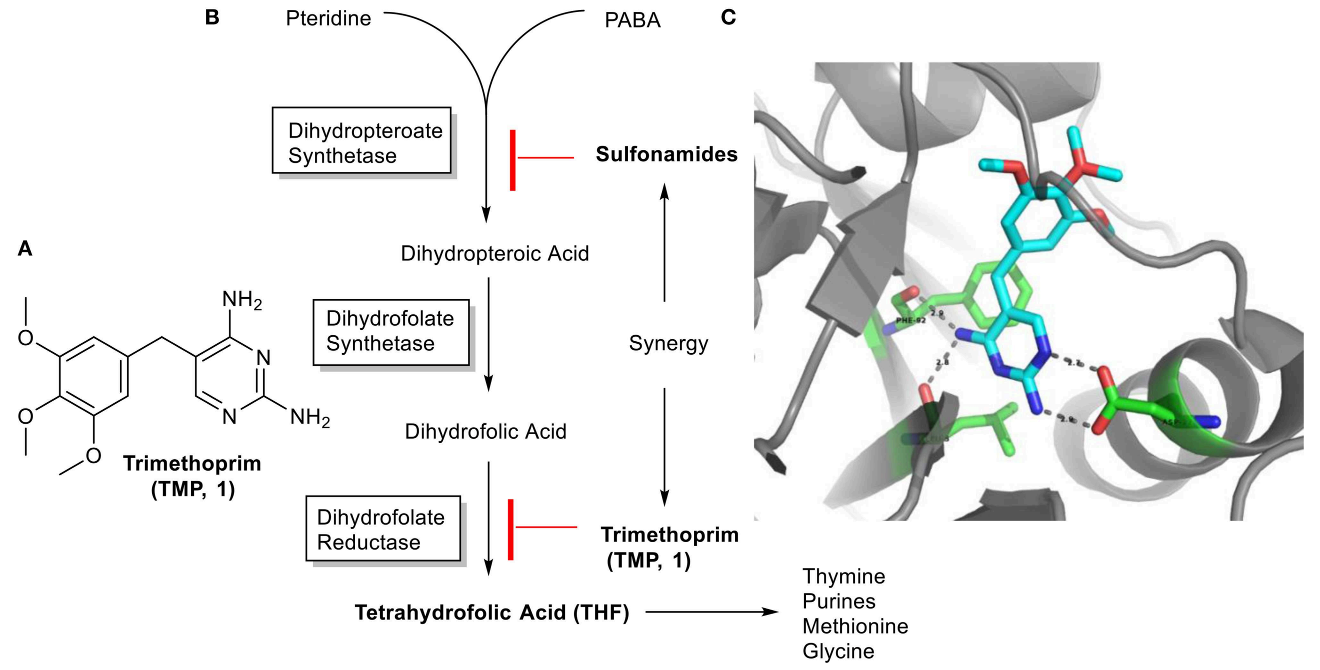


FIGURE 1 | (A) TMP (**1**) structure. **(B)** Folic acid biosynthetic route. **(C)** Interactions of the TMP (**1**, in blue) with key amino acid residues at the DHFR binding site. Representation based on the 2W9H PDB file, with a resolution of 1.48 A (Heaslet et al., 2009).

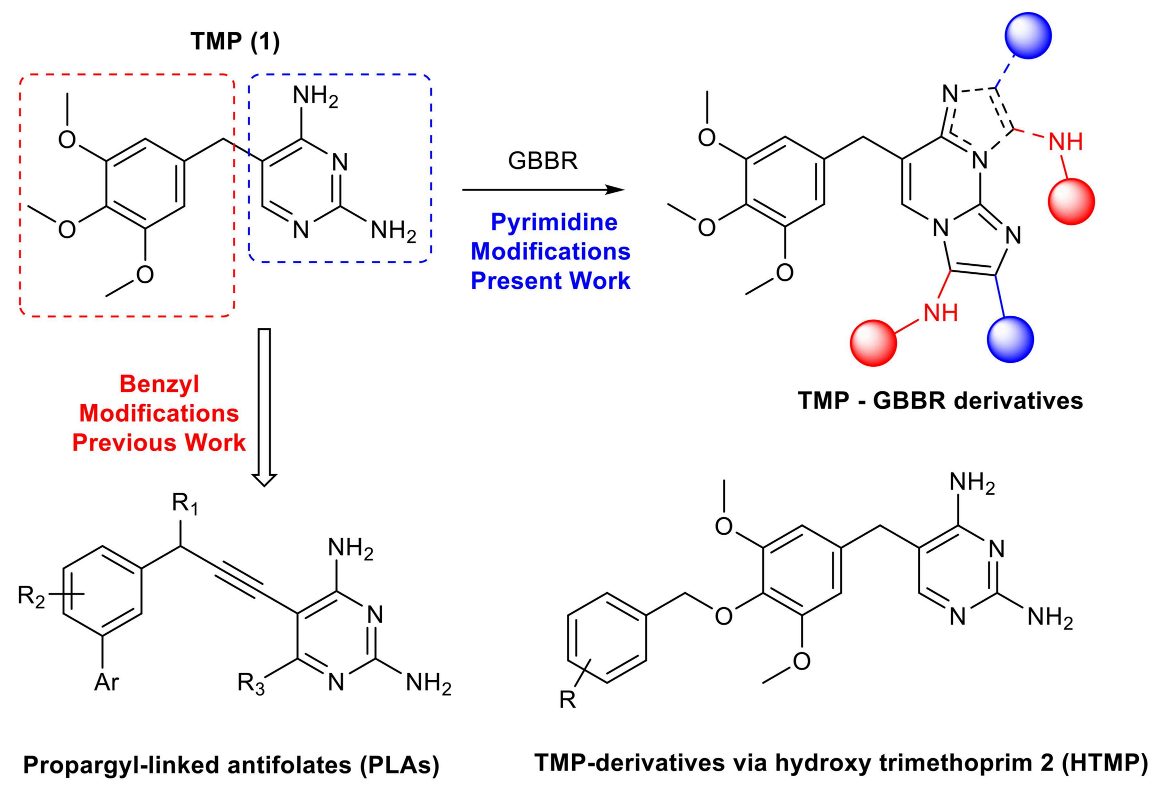
ineffective to treat infections of a subset of bacteria with TMP-resistant DHFR enzymes (Heaslet et al., 2009).

Thus, the exploration of new synthetic compounds mimicking the structure and mechanism of action of conventional antimicrobial agents can be regarded as a main goal of this field of research. Such chemical entities would open new perspectives to reduce secondary effects and to enhance antimicrobial action and/or spectrum. Moreover, interaction between new molecules and conventional antimicrobials should be explored with the aim to find eventual synergistic activity.

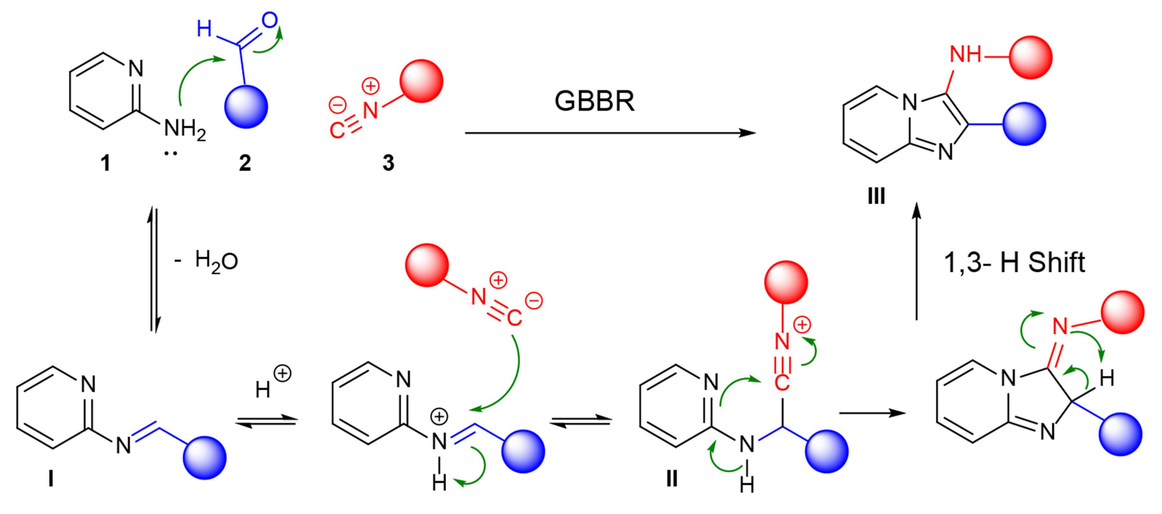
So far, some research groups have introduced chemical variability at the trimethoxybenzyl residue of the TMP in order to optimize the drug and improve its properties, overall activity and tackle TMP-resistance issues (**Scheme 1**) (Zhou et al., 2013; Lombardo et al., 2016; Rashid et al., 2016), being able to find promising potent compounds against *S. aureus* and *E. coli*. However, in this work we will focus our efforts on modifying the 2,4-diaminopyrimidine moiety, through a selective multicomponent reaction (MCR), the Groebke-Blackburn-Bienaymé reaction (GBBR). In the past, changes at this part of the molecule have not been considered, as they involve key interactions in the recognition of the natural substrate at the DHFR active site; however, the situation could be otherwise in mutated enzymes. Furthermore, inspection of the PDB of the crystal structure of a TMP-DHFR complex shows room for structural changes at the pyrimidine moiety (**Figure 1C**) (Heaslet et al., 2009). These GBBR-type modifications will change the heterocyclic core of the drug into a more complex di- or tricyclic azine, and up to four diversity points, which will be introduced in a regioselective manner (**Scheme 1**). These transformations, involving a relevant structural change on the TMP original framework, strictly speaking cannot be considered as drug late stage functionalizations (Cernak et al., 2016), although share the same philosophy of the approach.

MCRs represent an alternative to the usual sequential multistep synthesis. They involve the reaction of three or more starting materials in a convergent way to yield an adduct, whose structure embodies the major part of the reactive materials in a one-pot reaction through a unified mechanism (Zhu et al., 2014). Specifically, these reactions bring high efficiency, simplicity and both atom and step economy. Thus, they are of interest in medicinal chemistry to assemble relevant, complex heterocycles with remarkable bioactivities and to speed up the Structure-Activity Relationship studies (Hulme, 2005; Akritopoulou-Zanze and Djuric, 2010; Domling et al., 2012; Slobbe et al., 2012; Zarganes-Tzitzikas and Doemling, 2014).

The GBBR (**Scheme 2**) is an isocyanide-based MCR yielding azine-fused imidazoles from readily available aldehydes (**2**), isocyanides (**3**) and amidine-type building blocks (**1**) (Bienaymé and Bouzid, 1998; Blackburn et al., 1998; Groebke et al., 1998). Several reviews have abstracted the main features of this MCR (Devi et al., 2015; Pericherla et al., 2015). This important transformation is massively used in medicinal chemistry, especially in drug discovery, because of the drug like character of the adduct (imidazo-azine), together with the power to decorate it with a wide range of structural diversity (Shaaban and Abdel-Wahab, 2016). These *N*-fused bicyclic imidazo-azines represent a special class of privileged scaffold found in several bioactive compounds and commercially available drugs, such as Zolpidem, Alpidem, Necopidem, Zolimidine, Divaplon, and



SCHEME 1 | TMP-GBBR derivatives and precedent modifications on the benzyl moiety.



SCHEME 2 | Mechanism of GBBR.

Minodronic acid (approved for treatments of insomnia, anxiety, peptic ulcers, epilepsy, osteoporosis, etc.) (**Figure 2**). It is also well-known that α-polyamino-polyazines are important aromatic polyheterocycles present in a wide variety of clinical drugs, such as the antibacterial drug Trimethoprim, the anticonvulsant drug Lamotrigine and the anticancer drug Methotrexate. Furthermore, specific GBBR adducts have been identified as active antibiotics through phenotypic analyses, addressing a variety of targets (Al-Tel and Al-Qawasmeh, 2010; Shukla et al., 2012; Semreen et al., 2013; Kumar et al., 2014). These facts back our project to modify TMP via GBBR processes to deliver potentially useful novel antibiotics, either improving the activity of the original drug upon DHFR or acting through independent mechanisms.

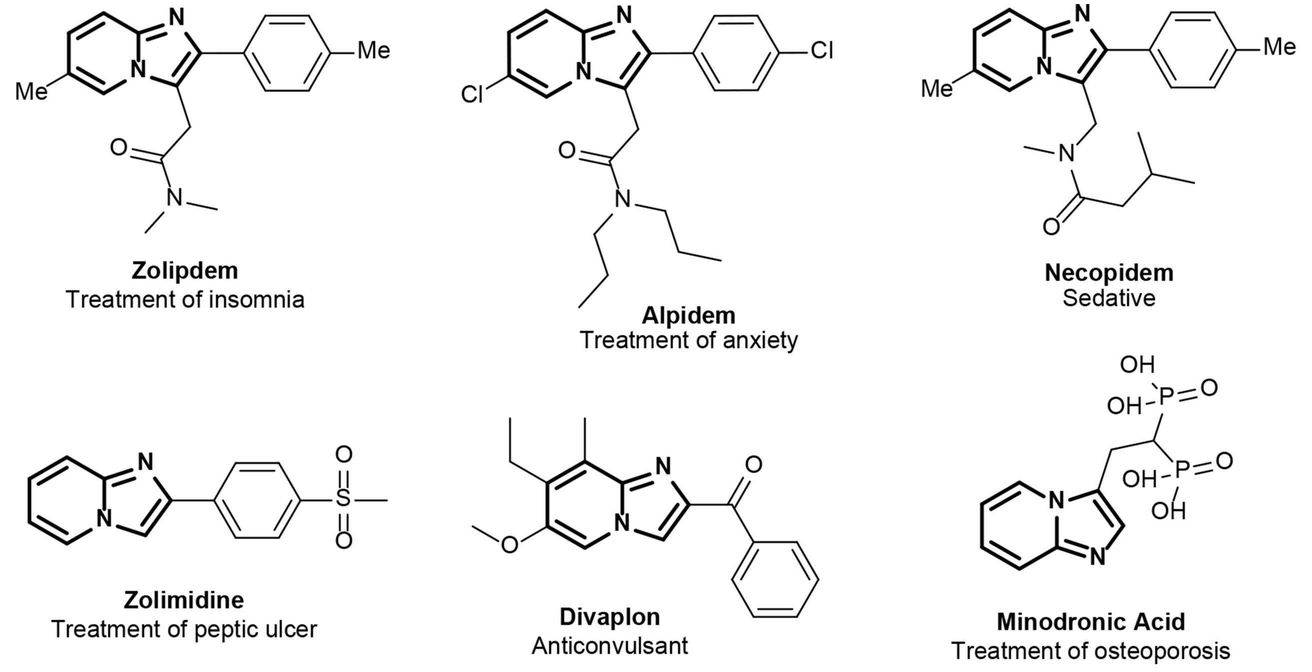


FIGURE 2 | Example of commercial drugs with *N*-fused bicyclic imidazo-azines. The imidazo-azine core is highlighted in bold.

RESULTS AND DISCUSSION

Chemical Synthesis

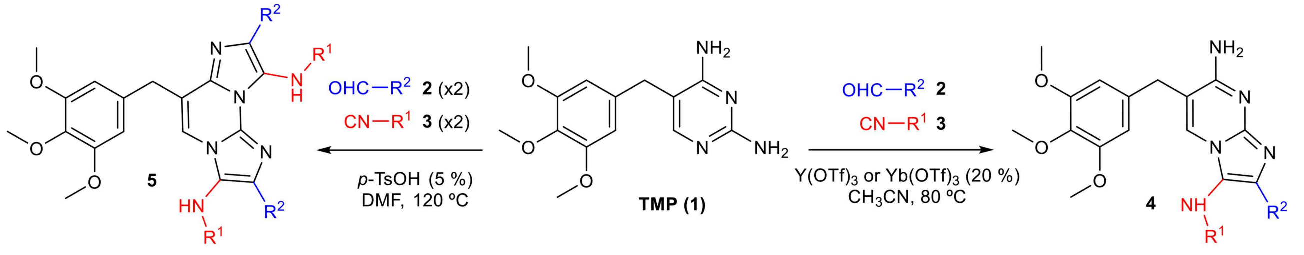
In this context, we planned to develop a series of TMP derivatives through the GBBR by interaction of the original drug (TMP, **1**) with a range of aldehydes (**2**) and isocyanides (**3**), and analyse the resulting MCR adducts as novel antibiotics, determining their potency, and efficiency, also considering their potential impact on resistant bacteria (**Scheme 3**).

The chemical modifications on TMP are based in our recent discoveries on GBBRs upon diaminopyrimidines, involving selective and multiple MCRs (Ghashghaei et al., 2018). In this way, the preparation of TMP analogs consisted in a regioselective mono-GBBR with an aldehyde/isocyanide pair, to yield derivatives **4**; it is worth mentioning that a kinetic control justifies the preferential formation of the observed isomer. Furthermore, double GBBR processes upon TMP yield doubly substituted derivatives **5**, with two equivalents of each reactant class (**Scheme 3**). The participation of a variety of Lewis acids catalyst is required to suitably generate and activate the imine intermediate and to achieve a moderate yield. In addition, standard flash chromatography purification was normally needed to afford the pure product. The designed analogs featured the *N*-fused bicyclic imidazo-azine scaffolds from the TMP reactant and displayed the variability points at substituents R^1, derived from the isocyanide input (**3**) and R^2 arising from the aldehyde reactant (**2**).

The processes worked in our TMP system as expected, yielding the corresponding products, showing the same reactivity and selectivity trends that were described in the unsubstituted diaminopyrimidine studies (Ghashghaei et al., 2018). For the initial screening, we prepared a series of TMP analogs featuring a variety of substituents on the imidazole amino group (R^1, being *tert*-butyl, 4-methoxyphenyl, cyclohexyl, and ethoxycarbonylmethyl) whereas at its carbon position a range of aromatic or alkyl substituents were introduced (R^2 being 4-chlorophenyl, α-, β-, or γ-pyridinyl, α-thienyl, methyl, and isopropyl). All the reactions were successful, yielding the mono-GBBR derivatives **4** and the doubly substituted-GBBR adducts **5** in acceptable yields (unoptimized). In this way, 12 new products (**4a**-**4j** and **5a**-**b**) arising from the corresponding aldehyde/isocyanide combinations were suitably prepared as pure materials (**Figure 3**).

The connectivity of the first analog synthesized (**4a**) was assigned through two-dimensional NMR experiments: HSQC, HMBC and NOESY spectra (see **Supplementary Material**) and matched with the expected structure, displaying the regioselectivity previously described (Ghashghaei et al., 2018). The rest of derivatives showed the same spectroscopical trends and their structures were assigned by analogy. Furthermore, the doubly substituted GBBR adducts **5** synthetically derived from the corresponding precursors **4**, then securing their identity.

We planned to incorporate an unsubstituted amino group in the imidazole ring of the novel derivatives **4** and **5** in order to favor their recognition by the DHFR active site, in line with the natural substrate. Then, we tackled the preparation of such compounds through the acidic removal of a *tert*-butyl group from a suitable precursor adduct coming from MCRs involving *tert*-butyl isocyanide. Precedent work by Krasavin et al. (2008) demonstrated that this transformation is feasible in GBBR



SCHEME 3 | Synthesis of mono- (**4**) and double- (**5**) TMP GBBR adducts.

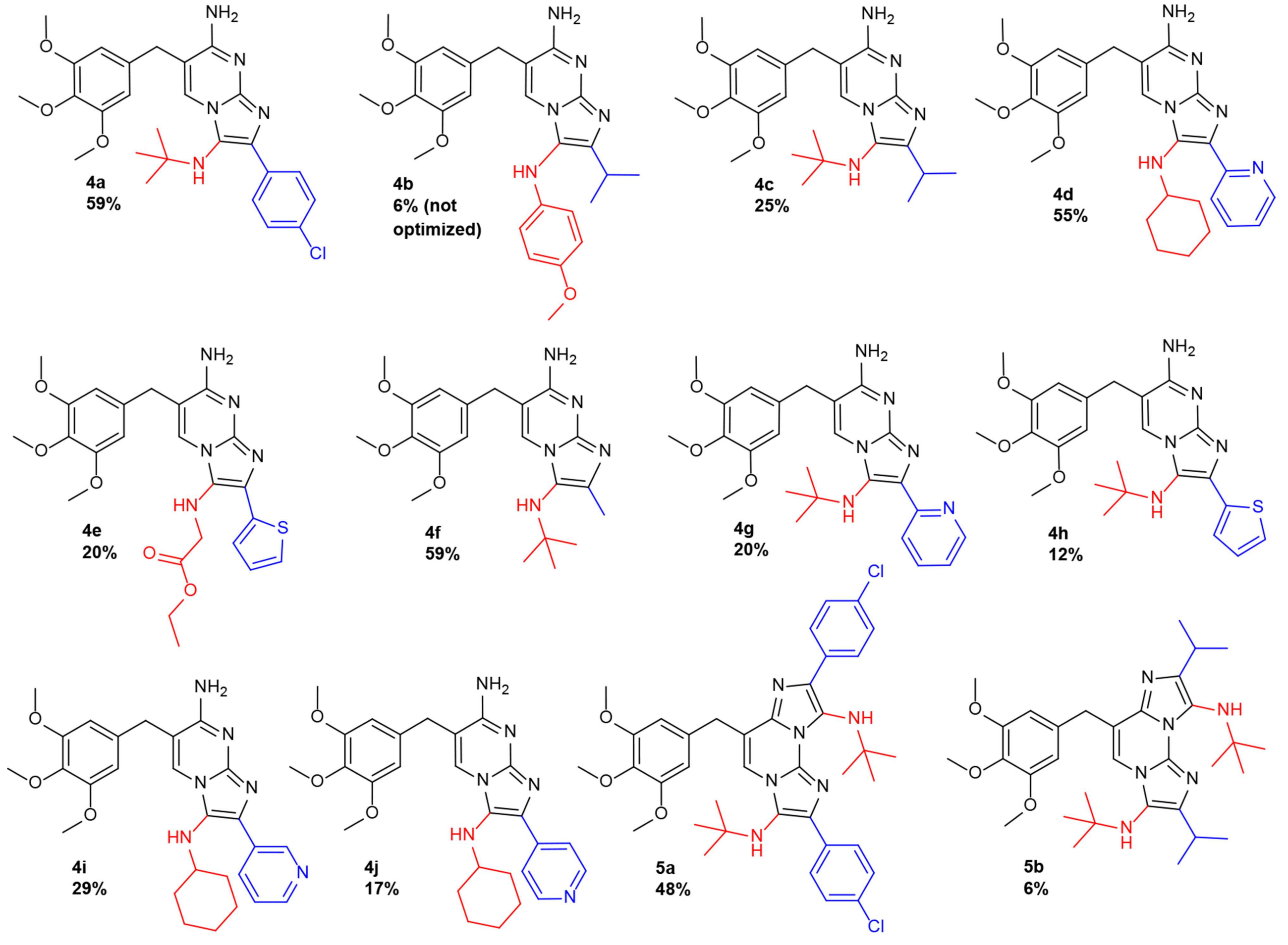
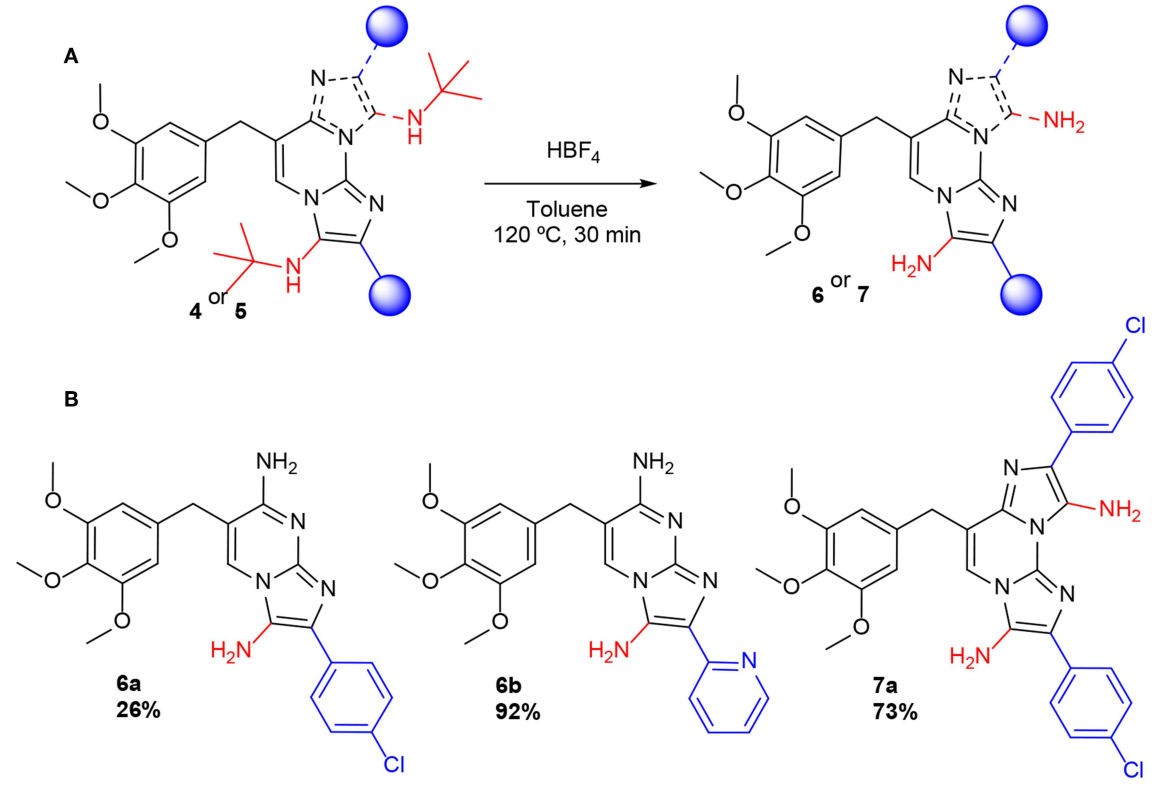


FIGURE 3 | TMP mono- (**4**) and double-GBBR (**5**) adducts.

adducts. In this way, compounds **6a-6b** and **7a** were obtained as pure unsubstituted amino derivatives form *tert*-butyl precursors **4** and **5**, after HBF_4 treatment (**Scheme 4**). All the synthesized compounds were suitably obtained in pure form, characterized and forwarded to microbiological analyses.

Biological Analyses

The Minimum Inhibitory Concentration (MIC) values of the 15 TMP analogs against control strains are shown in **Table 1** (for details, see the **Supplementary Material**). Although all the compounds showed MIC values against *E. coli* ATCC 25922 and *S. aureus* ATCC 29213 higher than TMP, some of them were almost as potent as TMP (**4c**, **4f**, **4h, 4i, 4j** and **6a**). *P. aeruginosa* PAO1 was found to be fully resistant to TMP, as well as to all new compounds. A preliminary inspection of the results showed that double GBBR adducts **5** lacked activity, probably meaning that they were unsuitable for binding to the target sites. Whereas for derivatives **4** some combinations were unproductive



SCHEME 4 | (A) Deprotection of N-*tert*-butyl groups in adducts **4** and **5**. **(B)** TMP-GBBR mono- (**6**) and double-adducts (**7**).

(especially the ones with aromatic and acetate R^1 substituents and *p*-chlorophenyl group at R^2 position), those featuring *tert*-butyl groups at R^1 and isopropyl, methyl, β-, γ- (but not α-) pyridyl, and α-thienyl groups at R^2 were particularly favored. Moreover, comparing compounds **4d**, **4g** and **6b**, we are able to confirm that the reduction of R^1 substituents size allowed to decrease the MIC. It is also worthy to emphasize that all compounds resulted to be more active on *E. coli* than on *S. aureus*; **4i**, **4c**, and **4f** being the most potent ones. Thus, chemical modifications do not seem to limit the ability of the different new compounds to penetrate the outer membrane in Gram negative bacteria.

Almost all the new compounds acted synergistically with SMX as the control drug TMP did, against *E. coli* ATCC 25922 and *S. aureus* ATCC 29213 (**Table 2**); the latter species being much more sensitive to the SMX combination than to the treatment with the TMP-GBBR analogs alone. It also becomes apparent that nearly all the new compounds presented high activity against a set of clinical isolates of MRSA isolated from hospitalized or Cystic fibrosis (CF) patients. In CF patients, *Staphylococcus aureus* (and particularly MRSA) infection is the main challenge of antibiotic therapy, since the persistent infection caused by this bacterium is strongly associated with increased rates of decline in respiratory function and high mortality (Dolce et al., 2019). Thus, new approaches to fight this kind of bacterium are mandatory and should be based on new antimicrobials, most probably combined with conventional ones (Lo et al., 2018; Xhemali et al., 2019).

Again, derivatives **4c**, **4f**, **4h**, **4i**, **4j**, and **6b** were the most potent, but interestingly, some adducts which were not meaningful acting alone (**Table 1**), on SMX combination displayed a relevant potency (**4a**, **4d**, **4e**, **4g**, and **6a**). Disappointingly, no effect either of adducts alone or in combination with SMX was observed on *Pseudomonas aeruginosa* in any case, in line with the detected TMP activity. Particularly interesting are the activities against MRSA isolates as can be seen in **Table 2**, with many derivatives being as active as the TMP reference.

A relevant feature in the use of an antibiotic is its kinetic profile. Specifically, a fast reduction of the growth rates of the infective microorganism is of capital interest in therapeutics, arguably as important or more than the effective dose. Thus, the effect of TMP analogs in combination with SMX on the growth curves of *E. coli* ATCC 25922 and *S. aureus* ATCC 29213 was studied for the most interesting compounds (**Figure 4** and **Supplementary Material**). Some differences were observed at subinhibitory concentrations of the antimicrobials (1/2 MIC and 1/4 MIC). In both tested bacteria, full inhibition occurred for derivatives **4g** and **4i** with SMX (1:20) at 1/2 the MIC value (**Figures 4A,C,D**). On the other hand, compounds **4g** and **4f**, at a concentration of 1/4 MIC, gave similar results than

TMP at 1/2 MIC against *E. coli* ATCC 25922 (**Figures 4A,B**). In all the cases, significant reductions in the growth rates were observed when compared with the antimicrobial-free control, being comparatively better for some conditions than the TMP reference, especially compound **4i** for long culture times (**Figure 4D**).

TABLE 1 | Minimum Inhibitory Concentration (MIC, μM) of TMP and the new GBBR analogs against *E. coli* ATCC 25922, *S. aureus* ATCC 29213, and *P. aeruginosa* PAO1.

	MIC (μM)		
	***E. coli* ATCC 25922**	***S. aureus* ATCC 29213**	***P. aeruginosa* PAO1**
TMP 1	0.43	13.78	> 110.22
4a	16.13	> 64.52	> 64.52
4b	> 67.01	> 67.01	> 67.01
4c	1.17	18.71	> 74.85
4d	8.19	> 65.50	> 65.50
4e	5.19	> 83.07	> 83.07
4f	1.25	80.10	> 80.10
4g	17.30	> 69.18	> 69.18
4h	2.14	> 68.44	> 68.44
4i	1.02	65.50	> 65.50
4j	2.05	65.50	> 65.50
5a	> 45.60	> 45.60	> 45.60
5b	> 56.66	> 56.66	> 56.66
6a	4.55	> 72.75	> 72.75
6b	2.46	78.73	> 78.73
7a	> 54.29	> 54.29	> 54.29

CONCLUSION

The marketed antibiotic TMP (**1**) has been succesfully modified by a GBB MCR with a range of commercially available aldehydes and isocyanides in selective processes yielding mono- or double- imidazo-azine adducts **4** and **5**. A short synthetic (one or two steps) protocol allowed access to a focused library of 15 TMP analogs featuring a novel heterocyclic scaffold with a relevant degree of chemical diversity at selected positions, including hydrogen atoms, small alkyl groups, aromatic and heteroaromatic rings. Incidentally, this work shows the possibility of using known drugs as substrates for MCRs and, in this manner, opens new ways to develop novel chemical entities of biological interest from this unusual origin. Antimicrobial activity of the novel analogs has been assayed in Grampositive (*S. aureus*) and Gramnegative (*E. coli*) microorganisms as well as on a bacterium considered the paradigm of resistance (*P. aeruginosa*). Despite the latter was resistant to all the new compounds, several mono-adducts **4** displayed MICs in the micromolar range against *E. coli* and *S. aureus*, what make us think that the TMP-derivatives bind to DHFR as well. The observed impact on growth kinetics allows us to conclude that the association of these new products with SMX exert a very similar effect than TMP itself. It is worthy to emphasize the excellent activities detected against MRSA strains. Given the reduced size of the focused chemset analyzed, and the relevant results found, we can conclude that the novel scaffold synthesized has potential to become a source for novel antibiotics. Further on going studies along these

TABLE 2 | Minimum Inhibitory Concentration (MIC, μM) of TMP and the new GBBR analogs in combination with Sulfamethoxazole (1:20) against *E. coli* ATCC 25922, *S. aureus* ATCC 29213, *P. aeruginosa* PAO1, *S. aureus* 8125304770, *S. aureus* 8139265926, *S. aureus* 8125255044, and *S. aureus* 8124825998.

	MIC (μM)						
	***E. coli* ATCC 25922**	***S. aureus* ATCC 29213**	***P. aeruginosa* PAO1**	***S. aureus* 8125304770**	***S. aureus* 8139265926**	***S. aureus* 8125255044**	***S. aureus* 8124825998**
TMP 1	0.11	0.43	13.78	0.431	0.86	0.22	0.43
4a	2.02	8.06	> 64.52	4.03	8.06	1.01	4.03
4b	67.01	> 67.01	> 67.01	67.01	> 67.01	67.01	> 67.00
4c	1.17	4.68	37.42	4.68	9.36	0.292	1.17
4d	2.05	4.09	> 65.50	4.09	4.093	1.02	4.09
4e	1.30	5.19	> 83.07	1.298	2.60	0.65	1.30
4f	0.63	5.01	40.05	0.63	2.50	0.63	1.25
4g	0.54	4.32	> 69.18	2.16	8.65	1.08	4.32
4h	0.27	2.14	34.22	1.07	1.07	0.27	1.07
4i	0.13	2.05	32.75	0.51	1.02	0.51	1.02
4j	0.26	2.05	32.75	1.02	2.05	0.51	1.02
5a	> 45.60	> 45.60	> 45.60	> 45.60	> 45.60	> 45.60	> 45.60
5b	28.33	> 56.66	> 56.66	28.331	> 56.66	14.17	56.66
6a	2.27	9.09	> 72.75	2.27	4.55	1.14	4.55
6b	0.31	2.46	78.73	1.23	2.46	0.62	2.46
7a	> 54.29	> 54.29	> 54.29	> 54.9	> 54.29	> 54.29	> 54.29

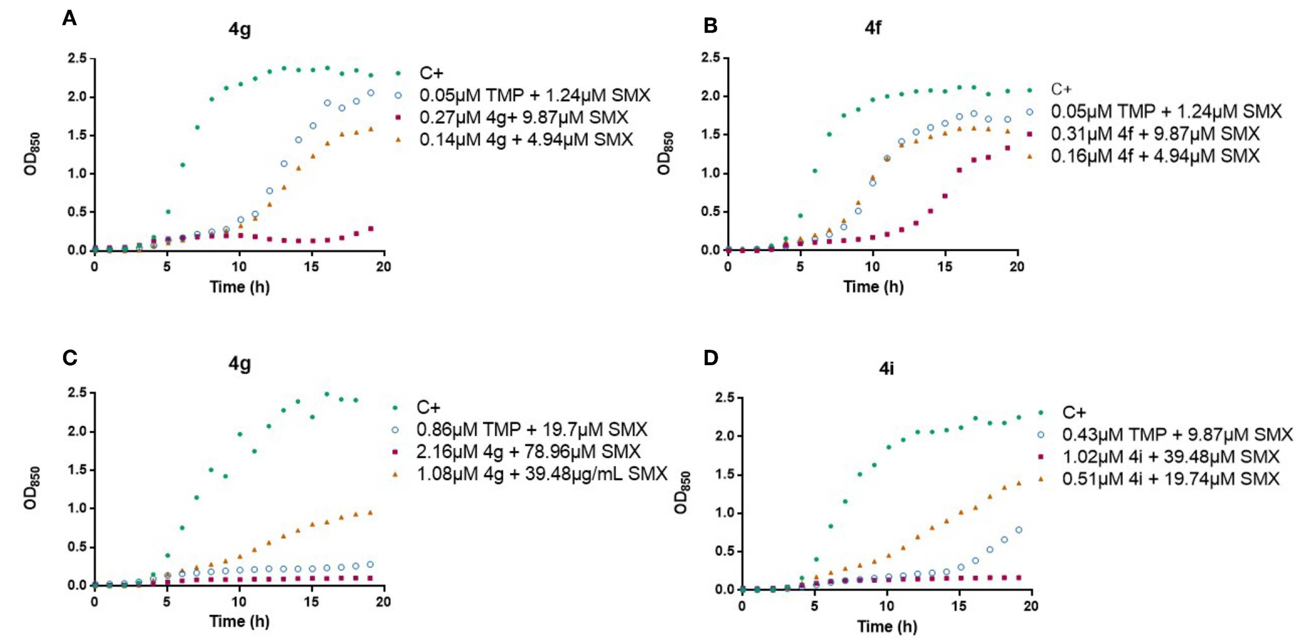


FIGURE 4 | Effect of the analogs **4f**, **4g**, **4i** and TMP in combination with sulfamethoxazole (1:20) on the growth curve of *E. coli* (**4g**, **4f**; **A,B**) and *S. aureus* (**4g**, **4i**; **C,D**).

lines tackle toxicity, the mechanism of action and bacterial resistance issues.

DATA AVAILABILITY

All datasets generated for this study are included in the manuscript and/or the **Supplementary Files**.

AUTHOR CONTRIBUTIONS

MP was responsible for designing and performing the initial experiments. EJ, FJ, OG, and RL performed the rest of the experimentation of the chemical section and analyzed the results. MJ designed and performed the microbiological experiments. MJ and MV analyzed the results of this section. All authors discussed the whole project and wrote the publication.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fchem.2019.00475/full#supplementary-material

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ORIGINAL RESEARCH
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Development of Novel and Efficient Processes for the Synthesis of 5-Amino and 5-Iminoimidazo[1,2-*a*]imidazoles via Three-Component Reaction Catalyzed by Zirconium(IV) Chloride

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General and efficient approaches for the synthesis of new 5-amino and 5-iminoimidazo[1,2-*a*]imidazoles were developed through a three-component reaction of 1-unsubstituted 2-aminoimidazoles with various aldehydes and isocyanides mediated by zirconium(IV) chloride. The protocols were established considering the reactivity of the starting substrate, which varies depending on the presence of a substituent on the 2-aminoimidazole moiety. A library of new N-fused ring systems with wide structural diversification, novel synthetic, and potential pharmacological interest was obtained in moderate to good yields.

Keywords: multicomponent reactions, isocyanide Ugi reaction, zirconium(IV) chloride, catalysis, N-heterocycles, fused-ring systems, 2-aminoimidazole

INTRODUCTION

The development of innovative synthetic approaches that allow rapid access to a wide variety of new heterocyclic derivatives is of crucial interest. The use of multicomponent reactions (MCRs) offers significant advantages in organic synthesis, such as the combination of chemical transformations of three or more different starting materials in a one-pot procedure without isolating the intermediates (Dömling and Ugi, 2000; Dömling, 2006; Abdelraheem et al., 2017; Bariwal et al., 2018; Murlykina et al., 2018). In 1998, the groups of Groebke, Blackburn, and Bienayme simultaneously developed a new subclass of MCRs to produce a series of azine- and azole-fused aminoimidazoles, using diverse 2-aminoazines or 2-aminoazoles, aldehydes and isocyanides in the presence of Lewis or Brønsted acid catalysts (Bienayme and Bouzid, 1998; Blackburn, 1998; Groebke et al., 1998).

This reaction recently attracted much attention in organic and medicinal chemistry because of its simplicity, efficiency and the ability to generate diverse compound libraries (Devi et al., 2015; Kaur et al., 2016; Shaaban and Abdel-Wahab, 2016; Shaabani and Hooshmand, 2016).

The fused bicyclic 5-5 systems containing three nitrogen atoms with one in the bridgehead position are an important class of fused heterocyclic compounds in organic and medicinal chemistry due to their relevant biological properties, such as anti-cancer (Baviskar et al., 2011; Grosse et al., 2014; Sidduri et al., 2014; Meta et al., 2017), anti-viral (Elleder et al., 2012), anti-inflammatory (Bruno et al., 2007; Brullo et al., 2012), and anti-diabetic effects (Mascitti et al.). Our group has been involved over the last few years in the development of powerful tools for the synthesis of such systems (El Akkaoui et al., 2012; Grosse et al., 2012, 2013, 2014; Arnould et al., 2013; Tber et al., 2015a,b; Driowya et al., 2018). For instance, we very recently reported an efficient one-pot three component procedure for the synthesis of new functionalized imidazo[1,2-*b*]pyrazole derivatives in addition to a library of hitherto undescribed 7,7′-(substituted methylene)bis-imidazo[1,2-*b*]pyrazoles starting from 3-aminopyrazoles, various aldehydes and isocyanides, using a catalytic amount of perchloric acid or zirconium(IV) chloride (Driowya et al., 2018).

The imidazo-imidazole scaffolds hold a special place in this category, since they are found in compounds showing a wide range of pharmaceutical activities. In particular, they have been described as antifungal (Lila et al., 2003), antithrombotic (Imaeda et al., 2008; Fujimoto et al., 2009), anxiolytic and anti-depressive agents (Han et al., 2005; Tellew and Luo, 2008; Zuev et al., 2010). In addition, they have been reported as androgen receptor agonists and antagonists that are useful in the treatment of a variety of disorders (Zhang et al., 2006). Several synthetic methods based on multistep synthesis have been employed by our group and others to prepare these medicinally important N-fused imidazoles (Langer et al., 2001; Poje and Poje, 2003; Adib et al., 2008; Saima et al., 2012; Chen et al., 2013; Grosse et al., 2015; Castanedo et al., 2016; Loubidi et al., 2016; Kheder and Farghaly, 2017).

On the other hand, compounds containing an imidazo[1,2-*a*]imidazole moiety have been understudied (Compernolle and Toppet, 1986; Kolar and Tisler, 1995; Mas et al., 2002). Only one paper was found in the literature for the preparation of 5-aminoimidazo[1,2-*a*]imidazole compounds by MCRs starting from 1,5-disubstituted 2-aminoimidazoles (Pereshivko et al., 2013). However, the reported protocol gave poor to moderate yields and showed some limitations with 1-unsubstituted 2-aminoimidazole substrates. Hence, there is a need to develop a new, more efficient and general method for the preparation of these derivatives.

In this context, and in continuation of our ongoing search for innovative small molecules, we report herein novel and straightforward approaches for the synthesis of new series of 5-amino and 5-iminoimidazo[1,2-*a*]imidazoles starting from 1-unsubstituted 2-aminoimidazoles and using zirconium(IV) chloride as catalyst. To the best of our knowledge, this is the first report using 1-unsubstituted 2-aminoimidazoles in MCRs.

RESULTS AND DISCUSSION

In order to find a MCR protocol that can afford an efficient formation of 5-aminoimidazo[1,2-*a*]imidazoles, we initially performed a model reaction using ethyl 2-aminoimidazole-4-carboxylate **1** with benzaldehyde and *t*-octyl isocyanide under different conditions (**Table 1**). Two possible regioisomers can be formed in this case **4a** or **4a′** according on which side of the 2-aminoimidazole **1** that reacts.

In our last study, we showed that the Lewis acid zirconium(IV) chloride delivered an efficient catalytic effect for the MCR (Driowya et al., 2018). This catalyst was therefore chosen for the present optimization study.

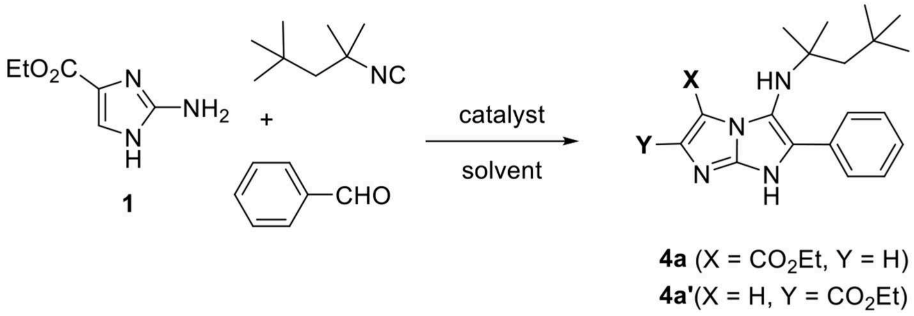
First, the reaction was carried out in methanol at room temperature in presence of 5 mol% of $ZrCl_4$, but unfortunately, no product was observed (entry 1). Poor yields of the expected product **4a** or **4a′** were obtained when the reaction was performed under heating in ethanol with either 5 or 10 mol% of $ZrCl_4$ (entries 2 and 3). The reaction time was significantly reduced to 10 min under MW irradiation at 140°C, and the yield was relatively improved to 38% (entry 4). The use of *n*-BuOH as solvent instead of EtOH under MW irradiation resulted in an improvement of the yield to 62% (entry 5), whereas the use of PEG-400 gave a moderate yield (entry 6). Interestingly, the reaction in PEG-400 under classical heating at 75°C during 4 h provided a very good yield (entry 7). Moreover, the optimal amount of catalyst (10 mol%) was confirmed, since the use of 5 mol% resulted in a lower yield (entry 8). Finally, replacing $ZrCl_4$ by other catalysts such as *p*-TsOH or $ZnCl_2$ was associated with a significant decrease in the yield of the product 5-aminoimidazo[1,2-*a*]imidazole **4a** or **4a′** (entries 9 and 10).

Hence, the optimized reaction conditions were found to be $ZrCl_4$ (10 mol%) as catalyst and PEG-400 as solvent with heating at 75°C during 4 h. This system was used before for the preparation of imidazo[1,2-*a*]pyridines (Guchhait and Madaan, 2009).

In order to disclose the structure of the formed regioisomer of this reaction, we carried out a single-crystal X-ray analysis of the product (**Figure 1**). The results reveal the formation of the regioisomer **4a**. The regioselectivity of this reaction can be explained by the presence of intermolecular hydrogen bonds on the ethyl 2-aminoimidazole-4-carboxylate **1**, orienting the synthesis toward the formation of only the regioisomer **4a**. Moreover, the structure of compound **4a** is stabilized by intramolecular N-H…O and intermolecular N-H...N interactions as observed in the crystalline structure (see the crystallographic section on the **Supplementary Material**).

With these reaction conditions in hand, we next explored the scope and limitation of our methodology with diverse 2-aminoimidazoles and isocyanides in the presence of a range of aldehydes as shown in **Table 2**. A large chemical library of 5-aminoimidazo[1,2-*a*]imidazole derivatives **4a–f** and **5a–i** was designed in generally good yields. The reactions proceeded well with both ethyl 2-aminoimidazole-4-carboxylate

TABLE 1 | Optimization of the reaction conditions.



Entry[a]	Catalyst (mol%)	Solvent	Temp (°C)	Heating method	Time	Yield (%)[b]
1	$ZrCl_4$ (5)	MeOH	r.t	–	14 h	0[c]
2	$ZrCl_4$ (5)	EtOH	80	Conventional	14 h	12[c]
3	$ZrCl_4$ (10)	EtOH	80	Conventional	14 h	18[c]
4	$ZrCl_4$ (10)	EtOH	140	MW	10 min	38
5	$ZrCl_4$ (10)	*n*-BuOH	140	MW	10 min	62
6	$ZrCl_4$ (10)	PEG-400	140	MW	10 min	31
7	**$ZrCl_4$ (10)**	**PEG-400**	**75**	**Conventional**	**4 h**	**77**
8	$ZrCl_4$ (5)	PEG-400	75	Conventional	6 h	55
9	p-TsOH (10)	PEG-400	75	Conventional	4 h	58
10	$ZnCl_2$ (10)	PEG-400	75	Conventional	7 h	23

[a] ***1*** *(1.0 mmol), benzaldehyde (1.1 mmol), t-octyl isocyanide (1.1 mmol), solvent (2 mL: entries 1–5; 1 mL: entries 6–10).*

[b] *Yield of isolated product.*

[c] *Starting materials were recovered.*

The bold values represent the optimized conditions.

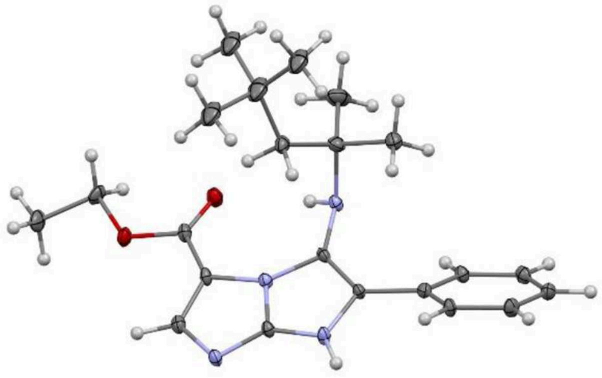


FIGURE 1 | ORTEP representation of compound **4a**.

1 and 4,5-dicyano-2-aminoimidazole **2**. Unfortunately, no reaction was observed when employing the unsubstituted 2-aminoimidazole **3** as substrate, which was recovered after purification.

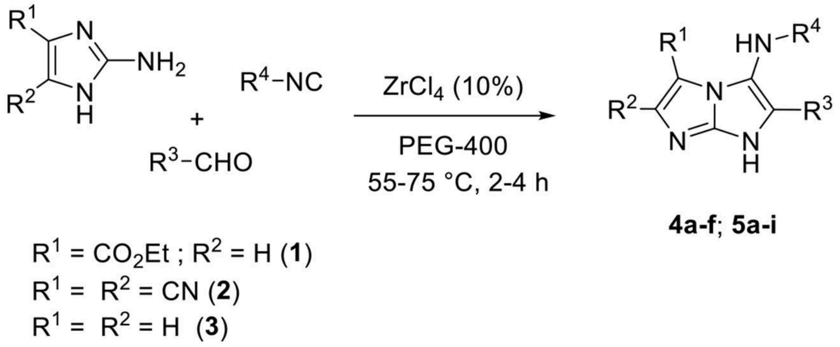
Moreover, the reaction occurred with electron-withdrawing and electron-donating substituents of the benzaldehydes, in addition to sterically hindered aldehydes (entry 9), aliphatic and heteroaromatic aldehydes (entries 12 and 13, respectively). However, a poor yield was obtained when using propionaldehyde (entry 12).

The impact of isocyanide on our reaction was also investigated; the *tert*-octyl isocyanide and *tert*-butyl isocyanide gave similar good results, whereas the cyclohexyl isocyanide showed slightly lower yields.

The MCR involving the unsubstituted 2-aminoimidazole **3** using our conditions did not yield any product. This can be explained by the poor reactivity of the starting substrate due to the absence of an electron-withdrawing group.

In order to find another strategy allowing us to synthetize 5-aminoimidazo[1,2-*a*]imidazoles starting from the unsubstituted 2-aminoimidazole **3**, we first carried out the condensation of the latter with *p*-anisaldehyde as a first step model reaction under different conditions (**Table 3**). The free amine **3** was prepared from the commercially available 2-aminoimidazole sulfate (see **Supplementary Material**). Initially, conventional or MW heating of the reaction in different solvents with $ZrCl_4$ (10 mol%) as catalyst provided the desired imine **6a** in poor yields (entries 1–4). The use of $ZnCl_2$ as catalyst furnished a very low yield (entry 5), while *p*-TsOH and $InCl_3$ gave slightly higher yields (entries 6 and 7). Very interestingly, using a reduced catalytic amount of $InCl_3$ (2 mol% instead of 10 mol%) under conventional or MW heating in ethanol produced a real improvement in terms of yield and reaction time (entries 9 and 11). This may explain the non-reactivity observed in the MCR

TABLE 2 | Synthesis of 5-aminoimidazo[1,2-*a*]imidazole derivatives **4a–f** and **5a–i**.



Entry[a]	R^1, R^2	R^3	R^4	Product	Yield (%)[b]
1	CO_2Et, H	C_6H_5	*t*-octyl	**4a**	77 (62)[c]
2	CO_2Et, H	4-$MeOC_6H_4$	*t*-octyl	**4b**	68
3	CO_2Et, H	4-ClC_6H_4	*t*-octyl	**4c**	56
4	CO_2Et, H	4-$CF_3C_6H_4$	*t*-octyl	**4d**	71
5	CO_2Et, H	C_6H_5	*t*-butyl	**4e**	74
6	CO_2Et, H	C_6H_5	cyclohexyl	**4f**	59 (50)[c]
7	CN, CN	C_6H_5	*t*-octyl	**5a**	67 (42)[c]
8	CN, CN	4-$MeOC_6H_4$	*t*-octyl	**5b**	65
9	CN, CN	2,4,6-$MeOC_6H_2$	*t*-octyl	**5c**	61
10	CN, CN	4-ClC_6H_4	*t*-octyl	**5d**	58
11	CN, CN	4-$CF_3C_6H_4$	*t*-octyl	**5e**	76
12	CN, CN	C_2H_5	*t*-octyl	**5f**	12 (5)[c]
13	CN, CN	3-Pyridyl	*t*-octyl	**5g**	79
14	CN, CN	4-ClC_6H_4	*t*-butyl	**5h**	60 (54)[c]
15	CN, CN	4-ClC_6H_4	cyclohexyl	**5i**	47
16	H, H	4-$MeOC_6H_4$	*t*-octyl	**-**	0 (0)[c]

[a] ***1**, **2**, or **3** (1.0 mmol), aldehyde (1.1 mmol), isocyanide (1.1 mmol), $ZrCl_4$ (0.1 mmol), PEG-400 (1 mL), 75°C, 4 h (entries 1–6, 16) or 55°C, 2 h (entries 7–15).*

[b] *Yield of isolated product.*

[c] *Isolated yield using the conditions: $ZrCl_4$ (10 mol%), n-BuOH (2 mL), MW (140°C), 10 min.*

(**Table 2**, entry 16), because of the instability of the formed imine under such acidic conditions. However, the prolonged reaction time noted with $ZrCl_4$ (2 mol%) or when no catalyst was used, revealed the influence of $InCl_3$ on this condensation reaction (entries 8 and 10, respectively).

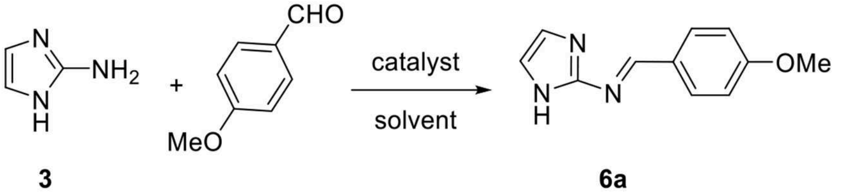
After developing these optimized conditions for the first reaction step, we next focused on finding the best conditions for the second step, which is based on the [4+1] cycloaddition reaction of the formed imine with an isocyanide.

The resulting imine **6a** was isolated and reacted with *tert*-octyl isocyanide under several catalytic conditions (**Table 4**). No reaction occurred when using the same conditions as for the condensation step (entry 1). Increasing the catalytic amount of $InCl_3$ to 10 mol% produced the desired product in poor yields with either conventional or MW heating methods (entries 2 and 3). It is interesting to note that the 5-aminoimidazo[1,2-*a*]imidazole product formed was unstable and underwent a dehydrogenation reaction *in situ* to generate the corresponding stable oxidized compound 5-iminoimidazo[1,2-*a*]imidazole **7a**. We already observed this type of oxidation in our previous work on the synthesis of imidazo[1,2-*b*]pyrazoles by MCRs (Driowya et al., 2018).

The use of other catalysts such as *p*-TsOH, $ZnCl_2$, and $ZrCl_4$ under microwave irradiation did not produce any significant improvement in the reaction yield (entries 4–6). However, using $ZrCl_4$ as catalyst and replacing EtOH by *n*-BuOH as solvent for the reaction showed a slight increase in the yield to 40% (entry 8), which was the optimum result obtained for this reaction. The same conditions used under conventional heating resulted in a significant decrease in the yield. The low yield and the difficulty of this reaction can be explained by the instability of the imine in the acid medium.

With these optimized conditions in hand, we succeeded in achieving the one-pot two-step procedure without isolating the imine by removing EtOH at the end of the first reaction step. The isolated product **7a** was obtained with a global yield of 32%. This protocol was next extended to the synthesis of series of 5-iminoimidazo[1,2-*a*]imidazoles **7a–i** starting from the unsubstituted 2-aminoimidazole and exploring a wide range of

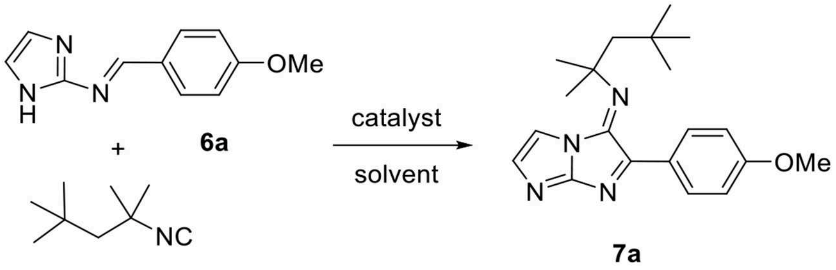
TABLE 3 | Screening conditions for the synthesis of imine **6a**.



Entry^a	Catalyst (mol%)	Solvent	Temp (°C)	Heating method	Time (h)	Yield (%)^b
1	$ZrCl_4$ (10)	PEG-400	75	Conventional	16	31
2	$ZrCl_4$ (10)	*n*-BuOH	140	MW	2	22
3	$ZrCl_4$ (10)	Toluene	110	Conventional	16	15
4	$ZrCl_4$ (10)	EtOH	80	Conventional	16	24
5	$ZnCl_2$ (10)	EtOH	80	Conventional	16	5
6	p-TsOH (10)	EtOH	80	Conventional	16	53
7	$InCl_3$ (10)	EtOH	80	Conventional	16	40
8	$ZrCl_4$ (2)	EtOH	80	Conventional	16	61
9	**$InCl_3$ (2)**	**EtOH**	**80**	Conventional	**2**	**78**
10	–	EtOH	80	Conventional	30	60
11	**$InCl_3$ (2)**	**EtOH**	**100**	**MW**	**1**	**75**
12	$InCl_3$ (2)	*n*-BuOH	100	MW	2	59

[a] ***3** (0.5 mmol), p-anizaldehyde (0.55 mmol).*
[b] *Yield of isolated product.*
The bold values represent the optimized conditions.

TABLE 4 | Screening conditions for the synthesis of 5-iminoimidazo[1,2-*a*]imidazole **7a**.

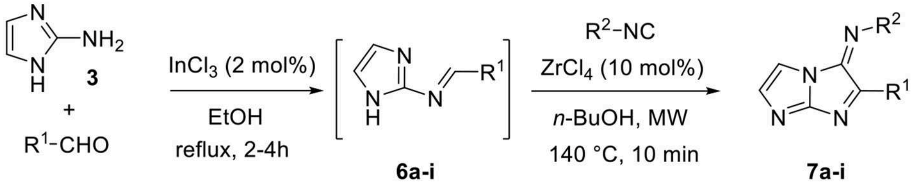


Entry^a	Catalyst (mol%)	Solvent	Temp (°C)	Heating method	Time	Yield (%)^b
1	$InCl_3$ (2)	EtOH	80	Conventional	14 h	0
2	$InCl_3$ (10)	EtOH	80	Conventional	6 h	<5
3	$InCl_3$ (10)	EtOH	140	MW	10 min	14
4	p-TsOH (10)	EtOH	140	MW	10 min	19
5	$ZnCl_2$ (10)	EtOH	140	MW	10 min	13
6	$ZrCl_4$ (10)	EtOH	140	MW	10 min	22
7	$ZrCl_4$ (10)	PEG-400	140	MW	10 min	26
8	**$ZrCl_4$ (10)**	*n*-BuOH	**140**	MW	**10 min**	**40**
9	$ZrCl_4$ (10)	*n*-BuOH	140	Conventional	3 h	<5
10	$ZrCl_4$ (5)	*n*-BuOH	140	MW	10 min	31
11	$InCl_3$ (10)	*n*-BuOH	140	MW	20 min	25

[a] ***6a** (0.2 mmol), tert-octyl isocyanide (0.22 mmol).*
[b] *Yield of isolated product.*
The bold values represent the optimized conditions.

aldehydes and isocyanides (**Table 5**). As mentioned previously, the 5-aminoimidazo[1,2-*a*]imidazole products formed were unstable and led directly to the corresponding imine forms **7a–i**. Despite the low yields obtained, it was nevertheless possible

TABLE 5 | One-pot two-step synthesis of 5-iminoimidazo[1,2-*a*]imidazole derivatives **7a–i**.

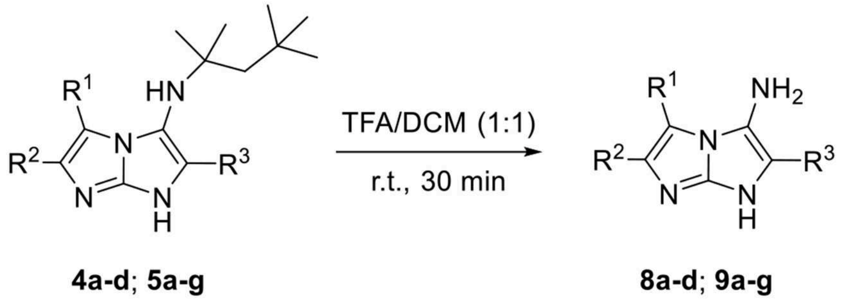


Entry[a]	R^1	R^2	Product	Yield (%)[b]
1	4-$MeOC_6H_4$	*t*-octyl	**7a**	32
2	C_6H_5	*t*-octyl	**7b**	24
3	2,4,6-$MeOC_6H_2$	*t*-octyl	**7c**	35
4	4-ClC_6H_4	*t*-octyl	**7d**	19
5	4-$CF_3C_6H_4$	*t*-octyl	**7e**	13
6	C_2H_5	*t*-octyl	**7f**	16
7	3-Pyridyl	*t*-octyl	**7g**	12
8	4-$MeOC_6H_4$	*t*-butyl	**7h**	17
9	4-$MeOC_6H_4$	cyclohexyl	**7i**	10

[a]***3*** *(1.0 mmol), aldehyde (1.1 mmol), $InCl_3$ (0.02 mmol), EtOH (10 mL), 2–4 h (90°C); isocyanide (1.1 mmol), $ZrCl_4$ (0.1 mmol), n-BuOH (2 mL), 10 min (140°C).*

[b]*Yield of isolated product.*

TABLE 6 | Cleavage of the *t*-octyl group of the products **4a–d** and **5a–g**.



Entry[a]	R^1	R^2	R^3	Product	Yield (%)[b]
1	CO_2Et	H	C_6H_5	**8a**	70
2	CO_2Et	H	4-$MeOC_6H_4$	**8b**	74
3	CO_2Et	H	4-ClC_6H_4	**8c**	68
4	CO_2Et	H	4-$CF_3C_6H_4$	**8d**	65
5	CN	CN	C_6H_5	**9a**	59
6	CN	CN	4-$MeOC_6H_4$	**9b**	61
7	CN	CN	2,4,6-$MeOC_6H_2$	**9c**	32
8	CN	CN	4-ClC_6H_4	**9d**	57
9	CN	CN	4-$CF_3C_6H_4$	**9e**	79
10	CN	CN	C_2H_5	**9f**	41
11	CN	CN	3-Pyridyl	**9g**	26

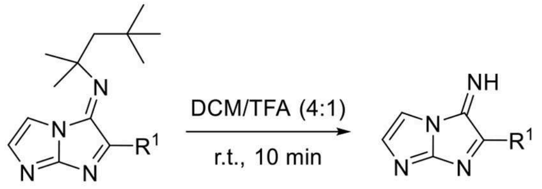
[a]***4a–d****, **5a–g** (0.2 mmol), DCM/TFA 1:1 (5 mL), r.t.*

[b]*Isolated yield.*

to produce the targeted compounds, which proved unsuccessful with the methods developed previously or with those cited in the literature.

The chemical space of our synthetized compounds was then enlarged, by removing the *tert*-octyl groups of 5-aminoimidazo[1,2-*a*]imidazoles **4a–d** and **5a–g** using TFA as cleavage agent in DCM and giving access to the primary amine compounds **8a–d** and **9a–g**, respectively, with yields ranging from 26 to 79% (**Table 6**). In a similar way, the primary imine imidazo[1,2-*a*]imidazoles **10a**, **10b**, **10d**, **10e,** and **10g** were

TABLE 7 | Dealkylation of the *t*-octyl group of the products **7a–g**.



7a-g

10a; 10b; 10d 10e; 10g

Entry[a]	R^1	Product	Yield (%)[b]
1	4-$MeOC_6H_4$	**10a**	74
2	C_6H_5	**10b**	85
3	2,4,6-$MeOC_6H_2$	–	–
4	4-ClC_6H_4	**10d**	82
5	4-$CF_3C_6H_4$	**10e**	63
6	C_2H_5	–	–
7	3-Pyridyl	**10g**	64

[a] ***7a–g*** *(0.15 mmol), DCM/TFA 4:1 (5 mL), r.t.*
[b] *Isolated yield.*

prepared in good yields from their corresponding Schiff base derivatives **7a, 7b, 7d, 7e,** and **7g** by deprotection of *tert*-octyl groups using the same conditions (**Table 7**). Unfortunately, the reaction was unsuccessful when the substituent R^1 was 2,4,6-trimethoxyphenyl (entry 3) or ethyl (entry 6).

CONCLUSION

In summary, we have designed highly efficient protocols of multicomponent isocyanide-based reactions catalyzed by zirconium(IV) chloride which offer the synthesis of a library of new functionalized 5-amino and 5-iminoimidazo[1,2-*a*]imidazoles in moderate to good yields. The optimized processes were successively applied to a large number of substituted (or unsubstituted) 2-aminoimidazoles, aldehydes and isocyanides. In addition, the use of inexpensive zirconium(IV) chloride as catalyst delivered an efficient catalytic effect for the reactions with a greater purity of isolated products compared to other catalysts.

DATA AVAILABILITY

All datasets generated for this study are included in the manuscript and/or the **Supplementary Files**.

AUTHOR CONTRIBUTIONS

MD designed and performed the experiments, then was responsible for writing the manuscript. RG realised the X-ray analysis for the compound **4a**. PB and GG directed the project and revised the manuscript.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fchem.2019.00457/full#supplementary-material

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A Mild, Fast, and Scalable Synthesis of Substituted α-Acyloxy Ketones via Multicomponent Reaction Using a Continuous Flow Approach

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A continuous flow approach for the synthesis of α-acyloxy ketone derivatives from the corresponding arylglyoxals, isocyanides, and carboxylic acids is described. The target products were obtained in excellent yields in short residence times and with high purities via the first transcription of the microwave-to-flow paradigm to the isocyanide-based Passerini reaction. Furthermore, this methodology allowed a 10-fold scale-up using the same experimental conditions initially established.

Keywords: continuous flow, α-acyloxy ketones, Passerini reaction, microwaves, multicomponent reactions

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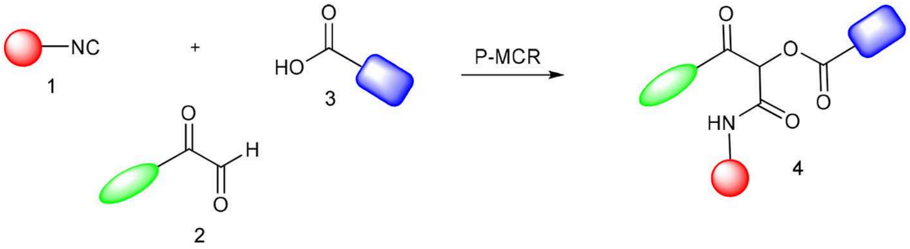
INTRODUCTION

Over the last decades, α-acyloxy ketones and their derivatives have become outstanding building blocks in organic synthesis due to their presence in several natural products and active pharmaceutical ingredients (APIs) (Prasad et al., 2018). Moreover, they participate in a wide range of synthetic transformations as starting materials or reactants, which result in important compounds such as cyclobutanes, aminoalcohols, hydroxy ketones, and heterocycles (furans, pyrroles, oxazoles, thiophenes, among others) (Shindo et al., 2007; Prasad et al., 2018).

Several reagents and reaction conditions to synthesize α-acyloxy ketones have been described in the literature (Prasad et al., 2018). However, most of them involve metal catalyzed oxidative coupling or electrophilic halogenations followed by nucleophilic displacement, which suffer from low atom economy and employ high amounts of oxidizing agents (Du et al., 2015; Hunter et al., 2016). Alternatively, functionalized α-acyloxy ketones may be easily accessed in a more sustainable way through the Passerini reaction (Neo et al., 2005, 2011).

The Passerini reaction is an efficient and versatile synthetic methodology and belongs to the class of isocyanide-based multicomponent reactions (IMCRs) (Dömling et al., 2012; Kazemizadeh and Ramazani, 2012). This one-pot reaction allows the obtention of α-acyloxy ketones bearing an α-carboxamide moiety from arylglyoxals, aldehydes and carboxylic acids (**Scheme 1**). In contrast to other processes described in the literature, this reaction not only offers an excellent atom economy without using oxidizing agents but also allows the obtention of functionalized products that can be explored in further transformations. However, the reported reaction times are longer (usually 2 to 3 days) and the Passerini products are obtained in moderate yields and in small scales (Neo et al., 2005, 2011). Compounds **4** are versatile intermediates and can be further converted to β-keto amides by Zn reduction in the presence of NH_4Cl.



SCHEME 1 | Synthesis of α-acyloxy ketones (4) through Passerini reaction between isocyanides (1), arylglyoxals (2), and carboxylic acids (3).

The continuous flow approach has been a relevant strategy in organic synthesis to access a plethora of compounds in a faster and scaled-up manner (Gutmann et al., 2015; Ley et al., 2015; Plutschack et al., 2017), including natural products and APIs (De Souza et al., 2018). Application of this strategy to IMCRs has already been described (Sharma et al., 2013; Heublein et al., 2014; Salvador et al., 2015; Vasconcelos et al., 2017) but its employment in Passerini reactions is still scarce (Sharma et al., 2013).

Herein, we describe a continuous flow approach for the synthesis of α-acyloxy ketone derivatives from the corresponding arylglyoxals, isocyanides and carboxylic acids. The first transcription of the microwave-to-flow paradigm (Glasnov and Kappe, 2011) toward the isocyanide-based Passerini MCR was used to access the target products in excellent yields, short residence times and with high purities through simple evaporation of the solvent at the end (Andrade and Dar, 2016). Furthermore, a 10-fold scale-up was accomplished using the same experimental conditions initially established.

RESULTS AND DISCUSSION

Batch Microwave Reaction Experiments

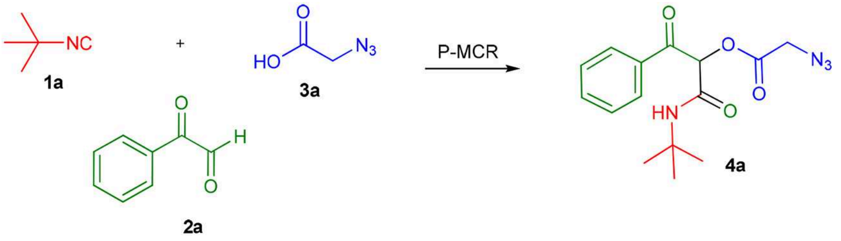
To evaluate the most appropriate reaction conditions for the synthesis of α-acyloxy ketones, an initial search for the best solvent was carried out in a batch microwave (MW) preliminary optimization using solvents typically applied in Passerini reactions (Wu et al., 2018) (**Table 1**) and considering our previous experience in MW-mediated MCR reactions (Barreto et al., 2011a,b, 2014; Salvador et al., 2015; Barreto and Andrade, 2018, 2019). Formation of the Passerini product in toluene at 110°C was not observed probably be due to the low microwave dielectric heating property of this solvent (Gabriel et al., 1998; Kappe et al., 2012) (entry 1). In $CHCl_3$ at 60°C, low conversions were observed (entry 2). However, using MeCN at this same temperature, a good conversion of the desired product was achieved (entry 3). In all cases, the applied experimental conditions were the same using equimolar amounts of the starting materials (0.5 mmol), 2 mL of solvent and reaction time of 30 min. Thus, MeCN was chosen as the best solvent for this reaction. Then, we decided to move forward and raise the temperature near the boiling point of MeCN (80°C). To our delight, at this temperature full conversion to product **4a** was achieved (entry 4). By decreasing the reaction time (entries 5–7), we found out that only 5 min were required for a full conversion of phenylglyoxal **2a** to product **4a**, which was isolated essentially pure in 94% yield (entry 7).

Converting Batch Microwave to Continuous Flow System

As already known, organic reactions performed in short times and well-established temperatures at microwave reactors are prone to be applied to a continuous flow setup device due to the effective residence time control and high thermal transfer achieved in this method (Damn et al., 2010; Kappe et al., 2013). With this in mind, we decided to transpose the microwave batch procedure just established for the synthesis of α-acyloxy ketones **4a** (**Table 1**, entry 7) into a continuous flow process (**Scheme 2**). Thus, a 0.5 M solution of *tert*-butyl isocyanide **1a** in MeCN (1 mL) in an injection loop (SL1) was mixed via a syringe pump in a flow rate of 0.5 mL min^{-1} (feed A in MeCN) with a 0.5 M solution of phenylglyoxal **2a** and azidoacetic acid **3a** (in 1 mL), which was pumped simultaneously from the second injection loop (SL2) at the same flow rate (feed B in MeCN). The combined solution possesses the same molar concentration (0.25 M) used in the microwave batch optimization and was pumped through a 5 mL perfluoroalkoxy (PFA) reactor coil (heated at 80°C in an oil bath) with outside (OD) and inner (ID) diameters of 1.6 and 0.8 mm, respectively. Additionally, a 3 bar back pressure regulator (BPR) was used to guarantee greater precision in the follow-up of the residence time. The design of the reactor capacity (5 mL) and the resulting flow rate (1 mL min^{-1}) furnished a total residence time unit (RTU) of 5 min (same reaction time used in the microwave optimization process). Satisfyingly, a similar and reproducible yield of compound **4a** was obtained with the continuous flow system as compared to the microwave-assisted synthesis. For comparison, the same reaction was carried out at room temperature and at reflux condition. The first condition gave the product in only 68% yield after 7 h (∼10% of non-reacted glyoxal). The second one gave the product in 94% yield but took 4 h to get to completion. Similar results were obtained for arylglyoxal **4c** bearing a strong electron donating group (*p*-OMe). These results show a significant improvement in the reaction outcome using the flow conditions developed in this study.

Inspired by these promising results, we decided to broaden the scope of this methodology and use this flow approach to synthesize various α-acyloxy ketones **4** using isocyanides **1a** and **1b**, arylglyoxals **2a-c**, and carboxylic acids **3a-g**. Numerous

TABLE 1 | Batch optimization of substituted α-acyloxy ketones synthesis using microwave heating[a].



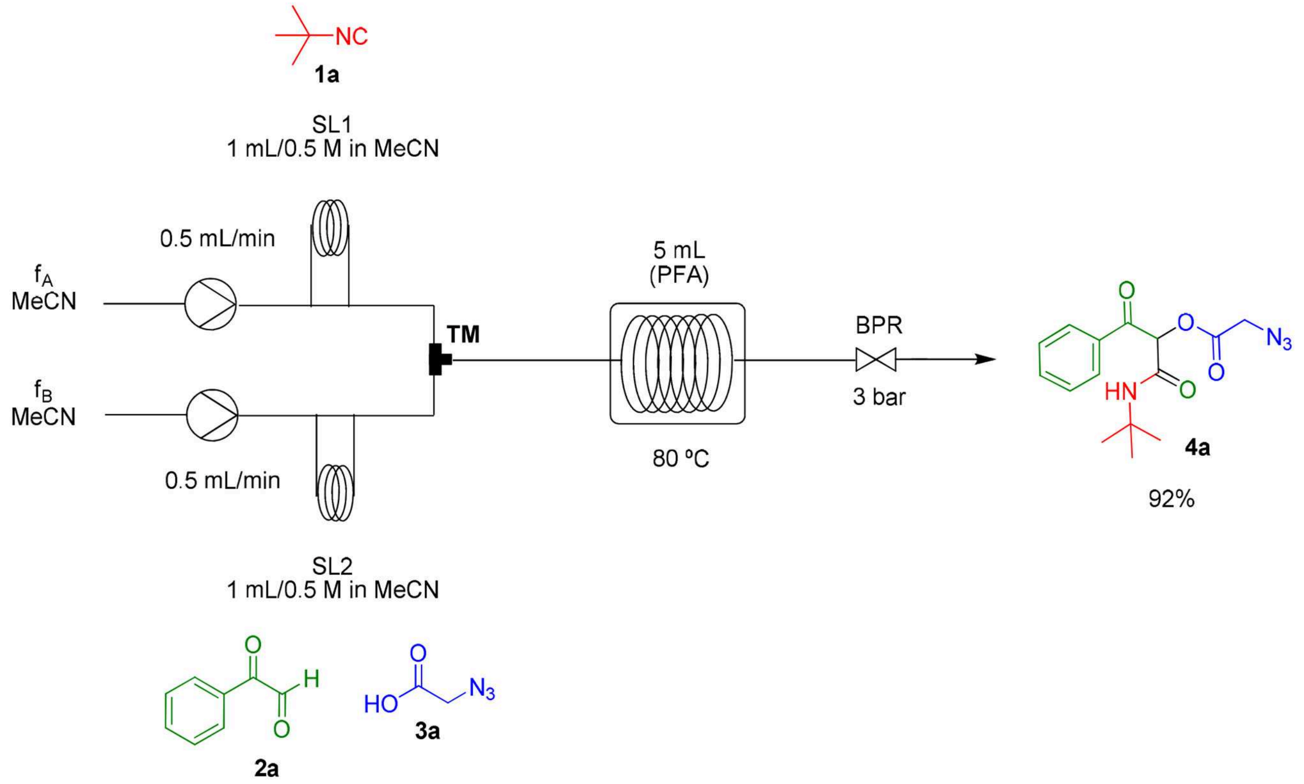
Entry	Solvent	T (°C)	Residence time (min)	Conversion (°C)[b]
1	Toluene	110	30	–[c]
2	$CHCl_3$	60	30	12
3	MeCN	60	30	70
4	MeCN	80	30	>99
5	MeCN	80	20	>99
6	MeCN	80	10	>99
7	MeCN	80	5	>99 (94)[d]

[a] *Conditions: reactions were carried out using equimolar amounts (0.5 mmol) of isocyanide* ***1a****, phenylglyoxal* ***2a*** *and azidoacetic acid* ***3a*** *in 2 mL of solvent.*

[b] *Determined based on phenylglyoxal* ***2a*** *and α-acyloxy ketone* ***4a*** *as HPLC-UV/VIS peak area percent at 215 nm.*

[c] *No product was observed.*

[d] *Isolated yield in parentheses.*



SCHEME 2 | Continuous flow synthesis of α-acyloxy ketone **4a**. Conditions: Feed A (1.0 mL of a 0.5 M solution of **1a** in MeCN) and feed B (1.0 mL of a 0.5 M solution of **2a** and **3a** in MeCN) pumped through a 5 mL PFA reactor at 80°C and 3 bar back-pressure regulator.

α-acyloxy ketones were obtained in excellent yields without the need for any re-optimization of the flowing experimental conditions (**Table 2**). All compounds from **Table 2** were isolated with high purity by a simple evaporation of the solvent (see NMR spectra in the **Supplementary Material**).

Scale-Up Process

Most organic reactions performed in traditional glassware usually work well at small-scale. Nevertheless, when an increase in scale is required, for instance for a chain development of distinct processes in pharmaceutical and fine chemicals, a great challenge arises in most cases due to inherent problems of scaling up processes such as heat generated and transferred, potential hazards of chemical compounds and environmental issues (Geyer et al., 2006). In contrast, the scale-up reaction performed in flow technology work very well due to the use of versatile approaches, which have similarities with the conditions used in small scale reactions (May et al., 2012, 2016). According to the features of flow processes, the scale-up synthesis of compound **4b** was used as a proof of concept and was achieved by increasing the length of the injection loop (2 mL) for better solubility of the starting materials and the length of the reactor coil (10 mL) to keep the same RTU used before (5 min). With these small adjustments, it was possible to achieve a reproducible 10-fold increase in the scale for the synthesis of compound **4b** in a productivity of 0.312 g/min (**Scheme 3**).

CONCLUSION

In summary, we have applied the first transcription of the microwave-to-flow paradigm for the isocyanide-based Passerini reaction to the synthesis of substituted α-acyloxy ketones via a continuous flow process. The target products can be further functionalized and were easily obtained in low residence times and excellent yields without the need for purification, which constitutes a significant improvement over the existing methods for preparing these compounds. Furthermore, the success of this methodology was corroborated by a 10-fold increase in the scale under similar reaction conditions leading to a productivity of 0.312 g/min.

EXPERIMENTAL PART

General Remarks

^{1}H-NMR spectra were recorded on a Varian Mercury Plus 300 MHz instrument. ^{13}C-NMR spectra were recorded on this same instrument at 75 MHz. Chemical shifts (δ) are expressed in ppm downfield from TMS as internal standard. The letters s, brs, t, dd and m are used to indicate singlet, broad singlet, triplet, double of doublets, and multiplet, respectively. HRMS experiments were performed on a TOF LC/MS instrument equipped with an ESI ion source (positive ionization mode) from Bruker. Analytical HPLC (Shimadzu LC20) analysis was carried out on a C18 reversed-phase (RP) analytical column (150 × 4.6 mm, particle size 5 μm) at 37°C using a mobile phase A (water/acetonitrile 90:10 (v/v) + 0.1% TFA) and B (MeCN + 0.1% TFA) at a flow rate of 1.5 mL/min. The following gradient was applied: linear increase from 30 to 100% B in 17 min. All microwave-mediated reactions were carried out in a CEM, Co. Discover microwave reactor in borosilicate closed glass reaction vessels (10 mL). For continuous flow procedures, KDS 210 Legacy dual syringe pump was used. Static backpressure, modular mixers, sample manual injectors, fittings, and tubings are commercially available from Idex Health & Science, Inc. All solvents and chemicals were obtained from standard commercial suppliers and were used without any further purification.

Starting Materials

2-azidoacetic acid (Yu et al., 2011), 3-azidopropionic acid (Yang et al., 2013), 2-oxo-2-phenylacetaldehyde, 2-(4-chlorophenyl)-2-oxoacetaldehyde and 2-(4-methoxyphenyl)-2-oxoacetaldehyde (Wang et al., 2013) were prepared and characterized according to literature procedures.

General Procedure for Batch Optimization of α-Acyloxy Ketones Synthesis Using Microwave Heating (Table 1)

A sealed 10 mL borosilicate glass reaction vessel, equipped with a magnetic stir bar and containing a mixture of equimolar amounts (0.5 mmol) of isocyanide **1a**, phenylglyoxal **2a,** and azidoacetic acid **3a** in 2 mL of MeCN was irradiated in a CEM Co. Discover reactor for 5 min at 80°C. After cooling to room temperature, the reaction mixture was concentrated under reduced pressure and the desired product (**4a**) was isolated in essentially pure form (entry 7).

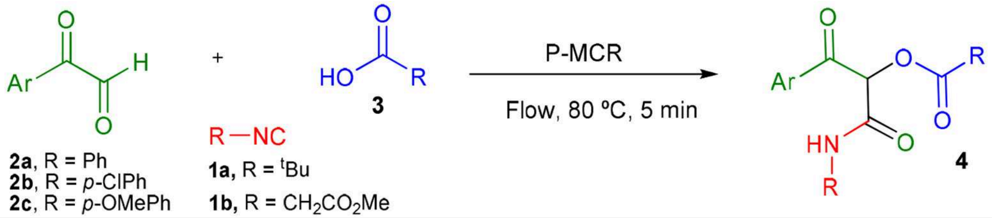
General Procedure for the Flow Synthesis of α-Acyloxy Ketones 4a to 4o

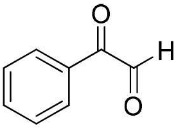
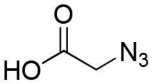
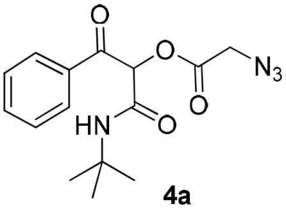
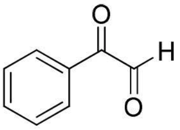
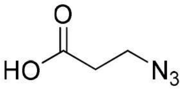
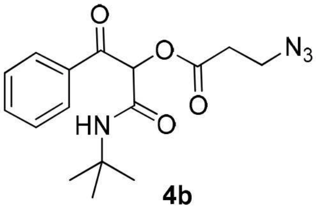
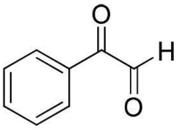
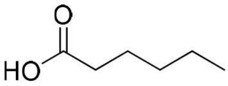
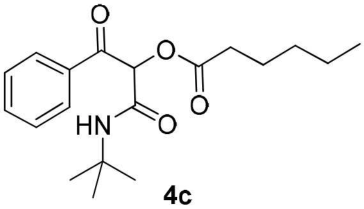
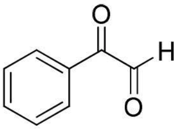
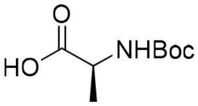
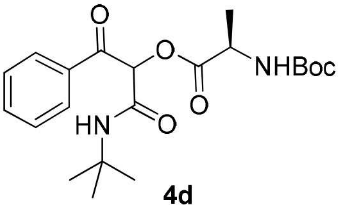
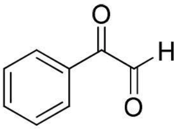
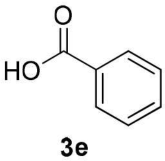
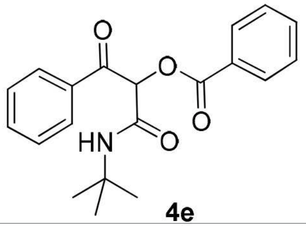
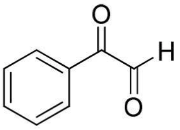
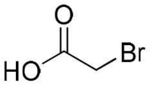
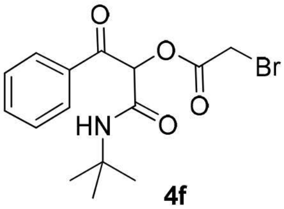
The PFA reactor coil (0.8 mm inner diameter; 5.0 mL) was completely filled with solvent (MeCN) and then heated in an oil bath at 80°C. Isocyanide **1a** (0.5 mmol) was diluted in 1.0 mL of MeCN (0.5 M) and stored in a 1 mL sample loop (SL1). Phenylglyoxal **2a** and azidoacetic acid **3a** (0.5 mmol each) were diluted in 1.0 mL of MeCN (0.5 M) and stored in a 1 mL sample loop (SL2). The sample loops were connected via a 6-way manual valve and were at the same time pumped into a T-shaped mixer (TM). After mixing, the resulting solution was fed (1 mL.min^{-1} stream) into the PFA reactor coil, thus remaining for 5 min of residence time under heating (80°C). A static back pressure regulator (3 bar) was used to allow the best fluid flow condition (Kappe et al., 2013). The desired products (**4a−4o**) were obtained after solvent evaporation under reduced pressure.

General Procedure for Continuous Flow Scale-Up for Synthesis of α-Acyloxy Ketone 4b

Same as above using 5.0 M solutions of compounds **1a**, **2a,** and **3b**, a 10.0 mL PFA reactor coil and 2 mL sample loops. Compound **4b** was obtained in 94% yield (1.56 g) with a productivity of 0.312 g/min (see **Scheme 3**).

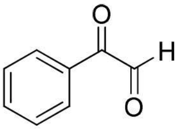
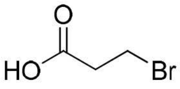
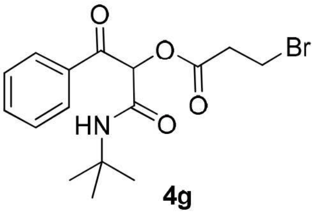
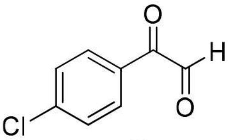
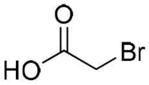
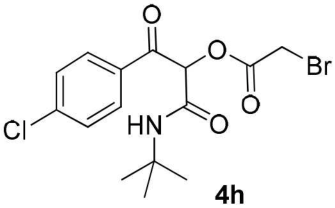
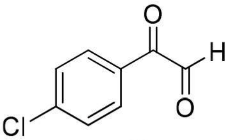
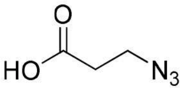
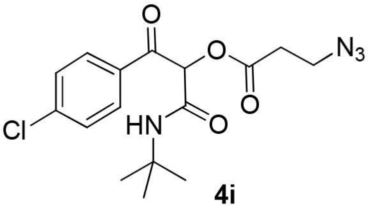
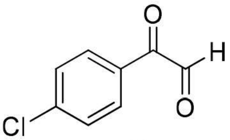
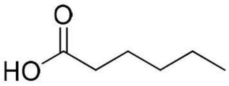
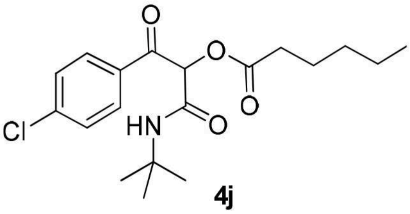
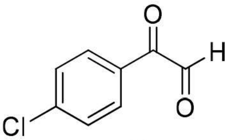
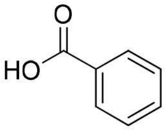
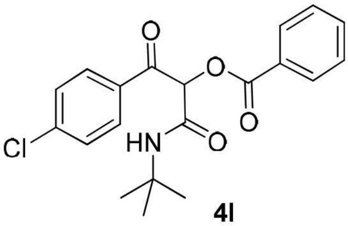
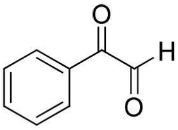
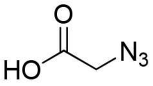
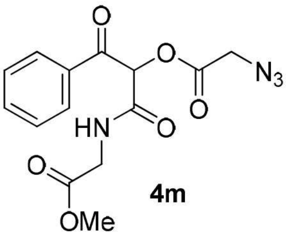
TABLE 2 | Scope for the Passerini-MCR flow synthesis of substituted α-acyloxy ketones.



Entry	RNC	Glyoxal	Acid	α-acyloxy ketone	Yield (%)
1	**1a**	 **2a**	 **3a**	 **4a**	92
2	**1a**	 **2a**	 **3b**	 **4b**	97
3	**1a**	 **2a**	 **3c**	 **4c**	93
4	**1a**	 **2a**	 **3d**	 **4d**	89
5	**1a**	 **2a**	 **3e**	 **4e**	94
6	**1a**	 **2a**	 **3f**	 **4f**	92

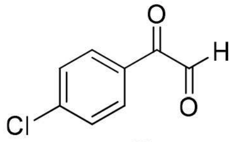
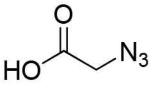
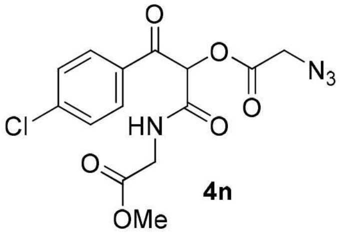
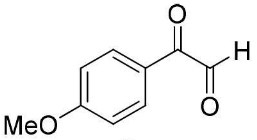
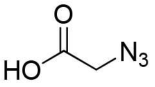
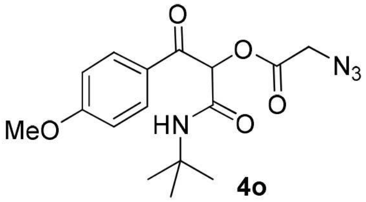
(Continued)

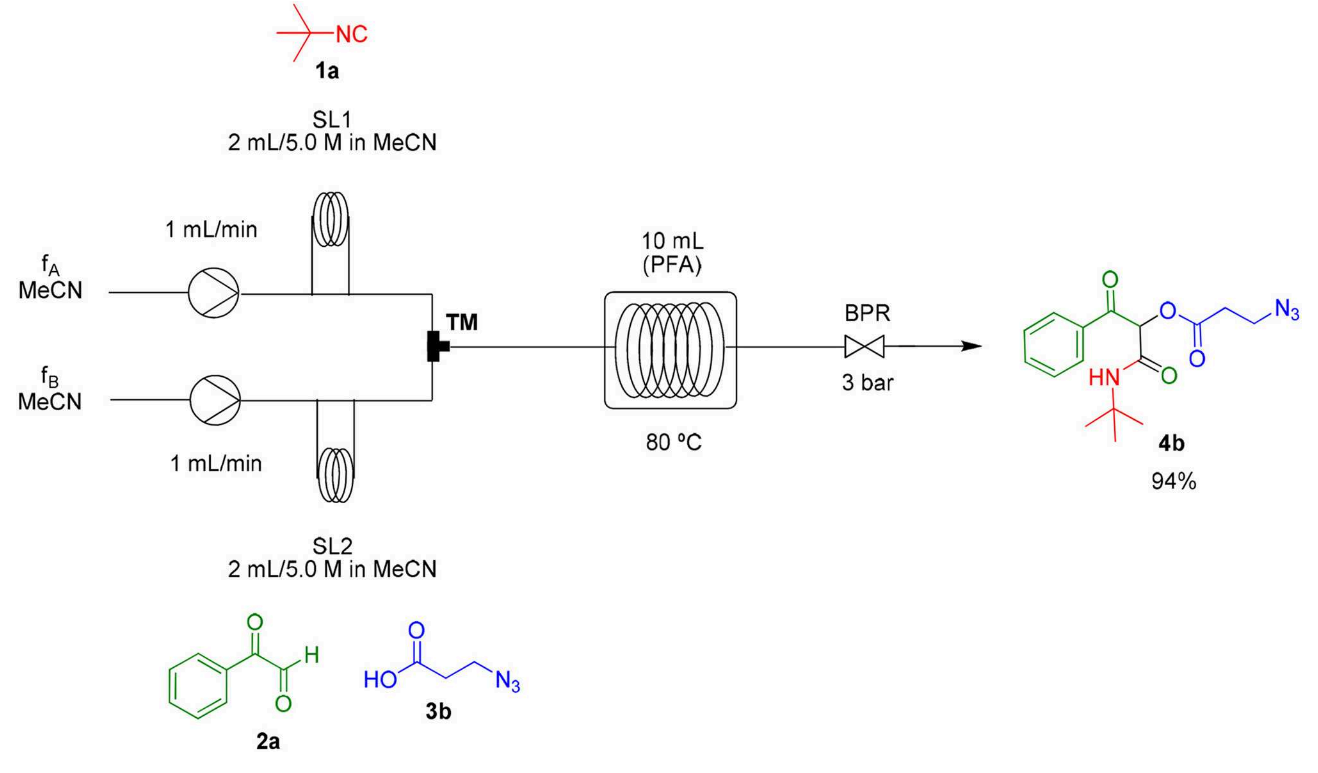
TABLE 2 | Continued

Entry	RNC	Glyoxal	Acid	α-acyloxy ketone	Yield (%)
7	**1a**	 **2a**	 **3g**	 **4g**	96
8	**1a**	 **2b**	 **3f**	 **4h**	95
9	**1a**	 **2b**	 **3b**	 **4i**	91
10	**1a**	 **2b**	 **3c**	 **4j**	95
11	**1a**	 **2b**	 **3e**	 **4l**	94
12	**1b**	 **2a**	 **3a**	 **4m**	89

(Continued)

TABLE 2 | Continued

Entry	RNC	Glyoxal	Acid	α-acyloxy ketone	Yield (%)
13	**1b**	 **2b**	 **3a**	 **4n**	90
14	**1a**	 **2c**	 **3a**	 **4o**	93



SCHEME 3 | Continuous flow scale-up for the synthesis of α-acyloxy ketone **4b**.

1-(*Tert*-Butylamino)-1,3-Dioxo-3-Phenylpropan-2-yl-2-Azidoacetate (4a)

Very viscous yellow oil (0.146 g, 92% yield); HRMS (ESI): m/z: calcd for $C_{15}H_{18}N_4O_4Na$ [M + Na^+]: 341.1220, found: 341.1226. ^1H-NMR (300 MHz, $CDCl_3$) δ (ppm) 8.17–8.10 (m, 2H), 7.67–7.58 (m, 1H), 7.54–7.46 (m, 2H), 6.30 (s, 1H), 6.14 (brs, 1H), 4.08 (s, 2H), 1.33 (s, 9H). ^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm) 191.3, 166.3, 161.7, 134.3, 134.1, 129.7, 128.7, 77.5, 52.2, 50.1, 28.4.

1-(*Tert*-Butylamino)-1,3-Dioxo-3-Phenylpropan-2-yl-3-Azidopropanoate (4b)

Very viscous yellow oil (0.161 g, 97% yield); HRMS (ESI): m/z: calcd for $C_{16}H_{20}N_4O_4Na$ [M + Na$^+$]: 355.1377, found: 355.1387. ^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm) 8.15–8.10 (m, 2H), 7.64–7.58 (m, 1H), 7.53–7.47 (m, 2H), 6.26 (s, 1H), 6.22 (brs, 1H), 3.61 (*t*, *J* = 6.2 Hz, 2H), 2.75 (*t*, *J* = 6.2 Hz, 2H), 1.34 (s, 9H). ^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm) 191.8, 168.8, 162.3, 134.3, 134.1, 129.6, 128.6, 76.5, 52.0, 46.4, 33.6, 28.4.

1-(*Tert*-Butylamino)-1,3-Dioxo-3-Phenylpropan-2-yl-Hexanoate (4c)

Very viscous colorless oil (0.155 g, 93% yield); HRMS (ESI): m/z: calcd for $C_{19}H_{27}NO_4Na$ [M + Na$^+$]: 356.1832, found: 356.1829; ^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm) 8.18–8.08 (m, 2H), 7.65–7.55 (m, 1H), 7.54–7.43 (m, 2H), 6.21 (s, 1H), 6.21–6.17 (brs, 1H), 2.54–2.44 (m, 2H), 1.74–1.59 (m, *2*H), 1.36–1.31 (m, 13H), 0.95–0.85 (m, 3H). ^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm) 192.5, 171.6, 162.8, 134.5, 134.0, 129.6, 128.5, 76.1, 51.9, 33.6, 31.1, 28.5, 24.3, 22.2, 13.8.

1-(*Tert*-Butylamino)-1,3-Dioxo-3-Phenylpropan-2-yl-(*Tert*-Butoxycarbonyl)-D-Alaninate (4d)

Very viscous brown oil (0.181 g, 89% yield); HRMS (ESI): m/z: calcd for $C_{21}H_{30}N_2O_6Na$ [M + Na$^+$]: 429.1996, found: 429.1998; Mixture of diastereomers: ^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm) 8.11–8.09 (m, 4H), 7.65–7.57 (m, 2H), 7.53–74.6 (m, 4H), 6.48 (brs, 1H), 6.35 (brs, 1H), 6.31 (s, 1H), 6.23 (s, 1H), 4.54–4.37 (m, 2H), 1.48–1.43 (m, 24H), 1.35 (*d*, *J* = 2.0 Hz, 18H). ^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm) 191.7, 191.5, 171.8, 170.9, 162.6, 162.6, 134.6, 134.4, 134.1, 134.0, 129.7, 129.7, 128.6, 128.6, 80.3, 76.4, 52.0, 49.1, 28.5, 28.5, 28.3, 28.5, 17.8, 17.7.

1-(*Tert*-Butylamino)-1,3-Dioxo-3-Phenylpropan-2-yl Benzoate (4e)

Very viscous yellow oil (0.170 g, 94% yield); HRMS (ESI): m/z: calcd for $C_{20}H_{21}NO_4Na$ [M + Na$^+$]: 362.1363, found: 362.1365; ^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm) 8.24–8.04 (m, 2H), 8.15–8.01 (m, 2H), 7.67–7.57 (m, 2H), 7.55–7.46 (m, 4H), 6.43 (s, 1H), 6.28 (brs, 1H), 1.39 (s, 9H). ^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm) 192.4, 164.6, 162.9, 134.6, 134.1, 133.9, 133.4, 129.7, 129.7, 128.7, 128.6, 76.8, 52.0, 28.6.

1-(*Tert*-Butylamino)-1,3-Dioxo-3-Phenylpropan-2-yl-2-Bromoacetate (4f)

Very viscous yellow oil (0.164 g, 92% yield); HRMS (ESI): m/z: calcd for $C_{15}H_{18}BrNO_4Na$ [M + Na$^+$]: 380.0296, found: 380.0296; ^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm) 8.13–8.10 (m, 2H), 7.66–7.59 (m, 2H), 7.55–7.47 (m, 2H), 6.27 (s, 1H), 6.26 (brs, 1H), 4.09–3.86 (m, 2H), 1.35 (s, 9H). ^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm) 191.9, 165.0, 162.0, 134.3, 134.2, 129.8, 128.6, 77.1, 52.1, 28.5, 24.8.

1-(*Tert*-Butylamino)-1,3-Dioxo-3-Phenylpropan-2-yl-3-Bromopropanoate (4g)

Very viscous colorless oil (0.178 g, 96% yield); HRMS (ESI): m/z: calcd for $C_{16}H_{20}BrNO_4Na$ [M + Na$^+$]: 392.0468, found: 392.0473; ^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm) 8.15–8.10 (m, 2H), 7.66–7.57 (m, 1H), 7.54–7.45 (m, 2H), 6.27 (s, 1H), 6.25 (brs, 1H), 3.61 (*t*, *J* = 6.6 Hz, 2H), 3.14 (*t*, *J* = 6.6 Hz, 2H), 1.34 (s, 9H). ^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm) 191.8, 168.5, 162.3, 134.4, 134.2, 129.7, 128.6, 76.5, 52.1, 37.2, 28.5, 25.1.

1-(*Tert*-Butylamino)-3-(4-Chlorophenyl)-1,3-Dioxopropan-2-yl-2-Bromoacetate (4h)

Very viscous colorless oil (0.186 g, 95% yield); HRMS (ESI): m/z: calcd for $C_{15}H_{17}BrClNO_4Na$ [M + Na$^+$]: 411.9922, found: 411.9918; ^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm) 8.12–8.06 (m, 8H), 7.51–7.44 (m, 8H), 6.24 (brs, 1H), 6.21 (s, 1H), 3.99 (m, 2H), 1.35 (s, 9H). ^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm) 190.0, 164.9, 161.8, 141.0, 132.6, 131.2, 129.3, 129.0, 128.8, 76.9, 52.2, 28.5, 24.7.

1-(*Tert*-Butylamino)-3-(4-Chlorophenyl)-1,3-Dioxopropan-2-yl-3-Azidopropanoate (4i)

Very viscous yellow oil (0.175 g, 91% yield); HRMS (ESI): m/z: calcd for $C_{16}H_{19}N_4O_4Na$ [M + Na$^+$]: 389.0987, found: 389.1002; ^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm) 8.12–8.06 (m, 2H), 7.51–7.44 (m, 2H), 6.25 (brs, 1H), 6.20 (s, 1H), 3.64 (*t*, *J* = 6.2 Hz, 2H), 2.78 (*t*, *J* = 6.2 Hz, 2H), 1.34 (s, 9H). ^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm) 190.7, 168.8, 162.1, 140.8, 132.7, 131.6, 129.0, 76.4, 52.1, 46.5, 33.6, 28.5.

1-(*Tert*-Butylamino)-3-(4-Chlorophenyl)-1,3-Dioxopropan-2-yl-Hexanoate (4j)

Very viscous yellow oil (0.175 g, 95% yield); HRMS (ESI): m/z: calcd for $C_{19}H_{26}ClNO_4Na$ [M + Na$^+$]: 390.1443, found: 390.1446; ^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm) 8.11–8.06 (m, 2H), 7.49–7.44 (m, 2H), 6.19 (brs, 1H), 6.14 (s, 1H), 2.54–2.45 (m, 2H), 1.73–1.59 (m, *2*H), 1.36–1.31 (m, 13H), 0.95–0.85 (m, 3H).^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm) 191.3, 171.5, 162.6, 140.5, 132.9, 131.1, 128.8, 75.9, 51.9, 33.6, 31.0, 28.4, 24.3, 22.2, 13.8.

1-(*Tert*-Butylamino)-3-(4-Chlorophenyl)-1,3-Dioxopropan-2-yl-Benzoate (4l)

Very viscous brown oil (0.176 g, 94% yield); HRMS (ESI): m/z: calcd for $C_{20}H_{20}ClNO_4Na$ [M + Na$^+$]: 396.0973, found: 396.0966; ^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm) 8.18–8.11 (m, 2H), 8.09–8.04 (m, 2H), 7.68–7.60 (m, 1H), 7.55–7.46 (m, 4H), 6.36 (s, 1H), 6.29 (bs, 1H), 1.39 (s, 9H). ^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm) 191.2, 164.5, 162.7, 140.7, 134.0, 132.9, 131.1, 129.8, 129.0, 128.7, 76.7, 52.1, 28.5.

1-((2-Methoxy-2-Oxoethyl)Amino)-1,3-Dioxo-3-Phenylpropan-2-yl-2-Azidoacetate (4m)

Very viscous colorless oil (0.151 g, 89% yield); HRMS (ESI): m/z: calcd for $C_{14}H_{14}N_4O_6$ $[M + H^+]$: 341.1220, found: 341.1226. ^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm) 8.14–8.10 (m, 2H), 7.66–7.61 (m, 1H), 7.54–7.47 (m, 2H), 6.47 (s, 1H), 6.47 (brs, 1H), 4.16–4.08 (dd, $J = 18.0, 6.0$ Hz, 1H), 4.12 (s, 2H), 3.99–3.91 (dd, $J = 18.0, 6.0$ Hz, 1H), 3.73 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 190.3, 169.4, 166.5, 163.2, 134.5, 133.8, 129.8, 128.7, 76.7, 52.6, 50.0, 41.1.

1-(4-Chlorophenyl)-3-((2-Methoxy-2-Oxoethyl)Amino)-1,3-Dioxopropan-2-yl-2-Azidoacetate (4n)

Very viscous yellow oil (0.168 g, 90% yield); HRMS (ESI): m/z: calcd for $C_{14}H_{13}N_4O_6Cl$ $[M + H^+]$: 369.0596, found: 369.0604. ^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm) 8.09–8.05 (m, 2H), 7.50–7.46 (m, 1H), 7.54–7.47 (m, 2H), 7.13 (brs, 1H), 6.42 (s, 1H), 4.16–4,08 (dd, $J = 18.0, 6.0$ Hz, 1H), 4.14 (s, 2H), 4.02–3.96 (dd, $J = 18.0, 6.0$ Hz, 1H), 3.95 (s, 3H). ^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm) 189.1, 169.4, 166.4, 163.0, 141.3, 132.1, 131.2, 129.1, 76.7, 52.7, 50.0, 41.1.

1-(*Tert*-Butylamino)-3-(4-Methoxyphenyl)-1,3-Dioxopropan-2-yl-2-Azidoacetate (4o)

Very viscous brown oil (0.162 g, 93% yield); HRMS (ESI): m/z: calcd for $C_{16}H_{20}N_4O_5$ $[M + Na^+]$: 371.1326, found: 371.1332. ^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm) 8.15–8.12 (m, 2H), 6.98–6.96 (m, 2H), 6.24 (brs, 1H), 6.12 (s, 1H), 4.10 (s, 2H), 3.90 (s, 2H), 1.33 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 189.3, 166.3, 164.6, 162.1, 132.3, 126.9, 113.9, 77.5, 55.5, 52.2, 50.1, 28.5.

DATA AVAILABILITY

All datasets generated for this study are included in the manuscript and/or the **Supplementary Files**.

AUTHOR CONTRIBUTIONS

CS was responsible for designing and performing the experiments and helped writing the publication. CA directed the project and wrote the publication.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fchem.2019.00531/full#supplementary-material

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Synthesis of Tris-Heterocycles via a Cascade IMCR/Aza Diels-Alder + CuAAC Strategy

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6-Triazolylmethyl-pyrrolo[3,4-*b*]pyridin-5-one tris-heterocycles were synthesized in 43–57% overall yields. The two-stage synthesis involved a cascade process (Ugi-3CR/aza Diels-Alder/*N*-acylation/aromatization) followed by a copper-assisted alkyne-azide [3+2] cycloaddition (CuAAC). This efficient and convergent strategy proceeded via complex terminal alkynes functionalized with a fused bis-heterocycle at the α-position. The final products are ideal candidates for SAR studies as they possess two privileged scaffolds in medicinal chemistry: 4-substituted or 1,4-substituted 1*H*-1,2,3-triazoles and pyrrolo[3,4-*b*]pyridin-5-ones.

Keywords: nitrogen tris-heterocycles, cascade IMCR process, CuAAC, Ugi-3CR, aza Diels-Alder

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INTRODUCTION

Polyheterocycles are organic molecules containing three or more heterocyclic moieties, which may be joined by one or more different kinds of connectivity (Ibarra et al., 2018). Nitrogen-containing polyheterocycles are of particular interest in the synthesis of bioactive molecules (Dener et al., 2006; Dolle et al., 2008; Atobe et al., 2013). Tris-heterocyclic molecules have been reported in optics and in coordination chemistry (Stibrany et al., 2003; Burling et al., 2007; Tahara et al., 2009).

The 4-substituted 1*H*-1,2,3-triazole is a heterocycle of high interest in medicinal chemistry, and it is well-documented that incorporation of this moiety into several bioactive compounds has resulted in advantages such as reduced toxicity or increased antibacterial or antimalarial activity (Shchepin et al., 2008; Zhou et al., 2008) [e.g., **Figure 1**, compound **A** (Dixit et al., 2012)]. Triazoles may also increase the stability and polarity of compounds by coordination of the N1 and N2 triazole nitrogens to active-site metal atoms in metalloproteases. The N3 nitrogen appears not to be directly involved in binding metals but can form hydrogen bonds with amino acid residues (Kallander et al., 2005; Huang et al., 2011; Röhri et al., 2012; Borkin et al., 2016). Additionally, 4-substituted 1*H*-1,2,3-triazoles are precursors of bioactive disubstituted 1,2,3-triazoles (Duan et al., 2009; Oh et al., 2010; Yan et al., 2010; Hsu et al., 2013; Bakulev and Beryozkina, 2016) and of pyridyl-1*H*-1,2,3-triazolate complexes that have applications in optics and coordination chemistry (Sinn et al., 2014; Prabhath et al., 2015). On the other hand, 1,4-disubstituted 1*H*-1,2,3-triazoles display structural and electronic similarities with the *trans*-amide bond. Their overall dipolar moment and hydrogen-bonding properties are greater than those of an amide bond, making these heterocycles effective peptidomimetics (Tron et al., 2008). These triazoles also function as flat bivalent elements, imitating the rigid conformational constraints of double bonds in alkyl chains. 1,4-Disubstituted 1*H*-1,2,3-triazoles are also capable substitutes for other five-membered nitrogen-containing heterocycles

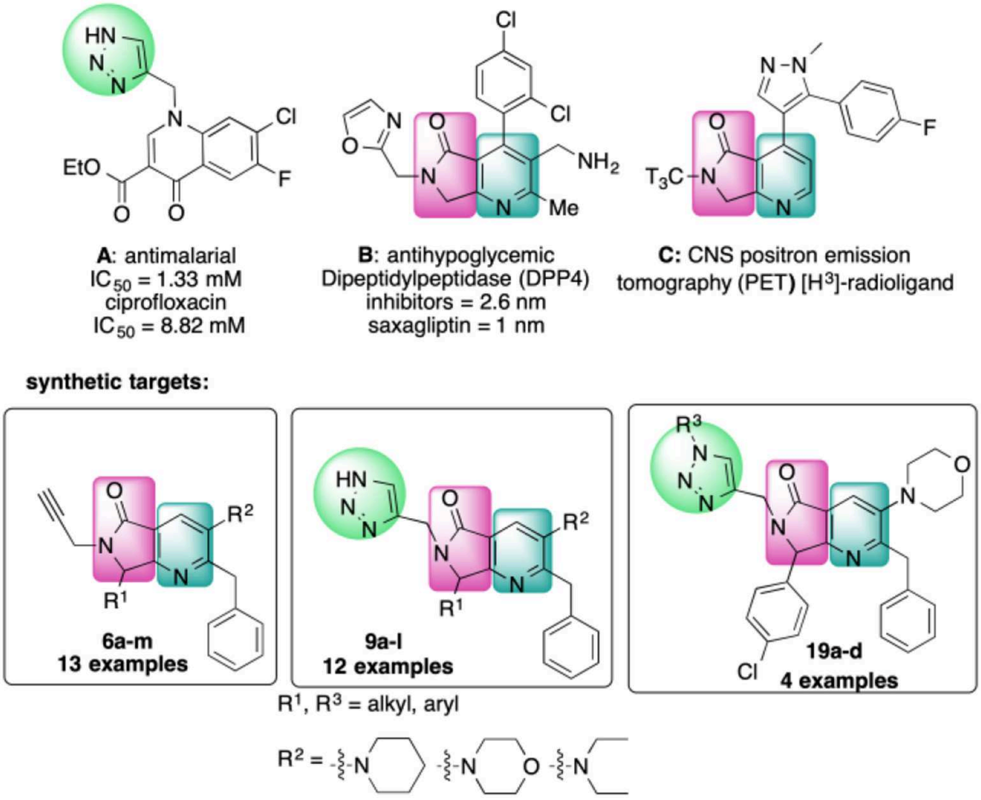


FIGURE 1 | Bioactive bis- and tris-heterocycles and our synthetic targets.

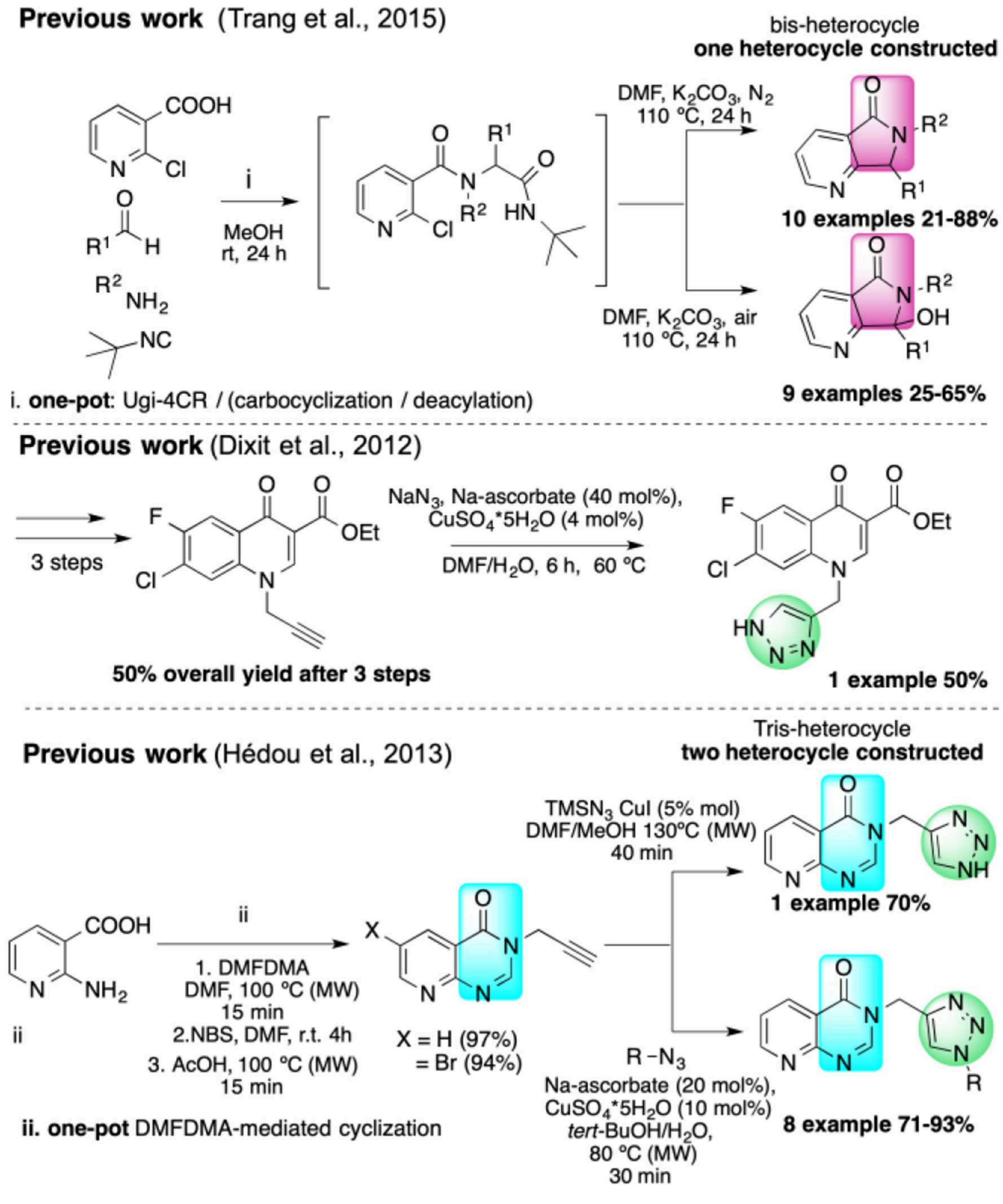
such as imidazoles, pyrazoles, 1,2,4-triazoles, oxazoles, isoxazoles, and oxazolidinones. Finally, these rings can act as more stable isosteres of phosphate linkers (Bonandi et al., 2017).

Common synthetic approaches to 4-substituted 1*H*-1,2,3-triazoles involve a [3+2] cycloaddition between sodium azide (NaN_3) or hydrazoic acid (HN_3) and terminal alkynes activated with electron-withdrawing groups (EWGs) (Hartzel and Benson, 1954; Balle et al., 2003; Blass et al., 2006; Koszytkowska-Stawińska et al., 2012). A variation of this classical methodology using trimethylsilyl azide ($TMSN_3$) provides a much safer procedure. The use of a copper(I) catalyst allows the use of non-activated terminal alkynes in shorter reaction times and under milder conditions (Jin et al., 2004). For preparing 1,4-disubstituted 1-*H*-1,2,3-triazoles, the classic synthetic approach is the regiospecific copper-assisted [3+2] cycloaddition between terminal alkynes with organic azides (Rostovtsev et al., 2002; Tornøe et al., 2002). The most common technique is *in situ* reduction of copper(II) salts, such as $CuSO_4 \bullet 5H_2O$ or $Cu(OAc)_2$, forming copper(I) salts using sodium ascorbate as the reducing agent. A second option is to use a copper(I) salt such as CuCl, CuBr, CuI, $[Cu(CH_3CN)_4]OTf$, or $Cu(CH_3CN)_4PF_6$ in a deoxygenated environment and in organic solvent, typically with an amine such as TEA, DIEA, DIPEA, or PMDETA (Bock et al., 2006; Hein and Fokin, 2010; Lauria et al., 2014).

On the other hand, the fused heterocycle pyrrolo[3,4-*b*]pyridin-5-one is an aza-analog of isoindolin-1-one natural products and is present in several bioactive molecules; for example: hypoglycemic [**Figure 1**, compound **B** (Devasthale et al., 2013)], analgesic, anticancer, and therapeutic agents for CNS-related diseases like Alzheimer's, epilepsy, and schizophrenia (Unverferth et al., 2002; Chang et al., 2008; Pajouhesh et al., 2012; Lindsley et al., 2013). The synthesis of analogs with a brain-selective radioligand has also been reported [**Figure 1**, compound **C** (Wager et al., 2017)].

There are no previous reports of molecules containing 4-substituted or 1,4-disubstituted 1*H*-1,2,3-triazoles and pyrrolo[3,4-*b*]pyridin-5-ones, though there are a few examples of each of these ring systems connected to other heterocycles using multistep approaches [**Figure 1**, compounds **A**-**C** (Dixit et al., 2012; Devasthale et al., 2013; Mallemula et al., 2015; Maračić et al., 2015; Wager et al., 2017)].

Isocyanide-based multicomponent reactions (IMCRs) are the most efficient strategies to synthesize pyrrolo[3,4-*b*]pyridin-5-ones, and Zhu first reported a one-pot synthesis in 2001 (Sun et al., 2001). We synthesized various annulated polyheterocycles containing this fused bis-heterocycle via IMCR strategies (Islas-Jácome et al., 2011, 2012). However, there are no published reports of pyrrolo[3,4-*b*]pyridin-5-ones linked to other heterocycles in a non-annulated fashion using IMCRs. Recently, Van der Eycken reported a one-pot synthesis of

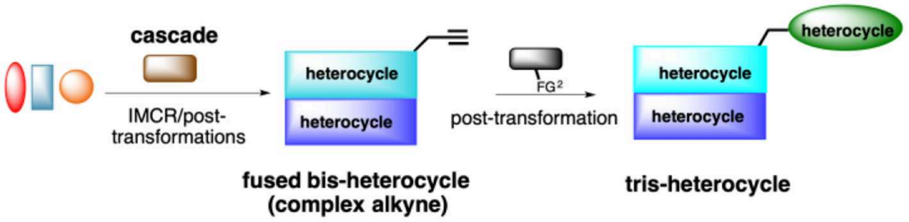


SCHEME 1 | Previous works.

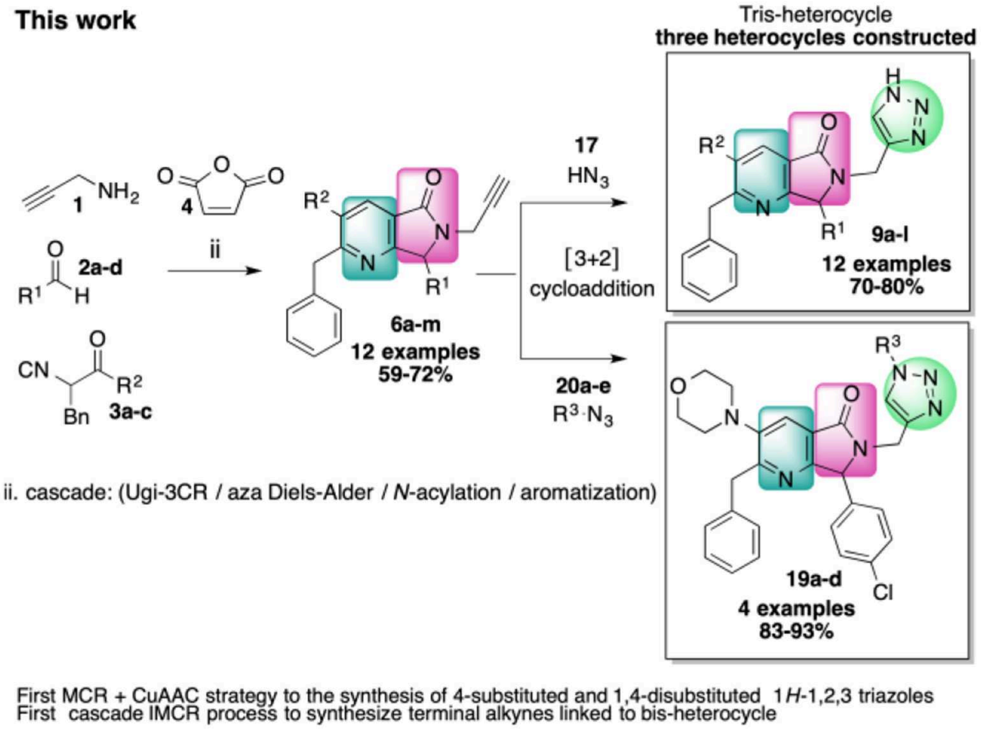
disubstituted pyrrolo[3,4-*b*]pyridin-5-ones by an Ugi four-component reaction (Ugi-4CR)/carbocyclization/deacylation sequence (**Scheme 1**; Trang et al., 2015). While that work can generate oxidized 7-hydroxy derivatives, we sought a route that would feature improved atom economy, shorter reaction times, and milder conditions in addition to greater structural complexity with more functionalized products (**Scheme 1**).

Besson reported the two-stage synthesis of tris-heterocycles with pyrido[2,3-*d*]pyrimidin-4(3*H*)-one linked to 1,2,3-triazoles via a one-pot DMFDMA-mediated cyclization followed by a CuAAC (**Scheme 1**; Hédou et al., 2013). However, only two heterocycles are constructed in this process and the scope of the alkynes is limited.

Our ongoing research program focuses on the design of rapid, convergent and efficient IMCR/post-transformation



SCHEME 2 | Cascade IMCR /[3+2] cycloaddition strategy.



SCHEME 3 | Synthesis of 4-substituted 1*H*-1,2,3-triazoles **9a-l** and 1,4-disubstituted 1*H*-1,2,3-triazoles **19a-l** via an IMCR/aza Diels-Alder/*N*-acylation/aromatization/[3+2] cycloaddition sequence.

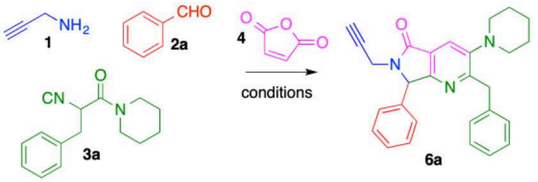
strategies toward novel molecules containing privileged heterocycles: azepino[4,5-*b*]indol-4-ones (Rentería-Gómez et al., 2016b), 2-tetrazolylmethyl-isoindolin-1-ones (Rentería-Gómez et al., 2016a), tetrazolo[1,5-*a*]quinolines (Unnamatla et al., 2016), 3-tetrazolylmethyl-azepino[4,5-*b*]indol-4-ones (Gordillo-Cruz et al., 2013), 2,3,4,9-tetrahydro-1*H*-β-carbolines (Cárdenas-Galindo et al., 2014), 4-(pyridine-3-yl)pyrimidines (Cortes-García et al., 2016), and spiro[pyrrolidine-3,3′-oxindoles] (Alvárez-Rodríguez et al., 2018). Herein we describe the first cascade IMCR process/post-transformation strategy toward the synthesis of 4-substituted 1*H*-1,2,3-triazoles linked to a fused, bis-heterocyclic peptidomimetic. A key aspect of this work is that the cascade IMCR process rapidly generates a complex alkyne for the subsequent [3+2] cycloaddition (**Scheme 2**).

RESULTS AND DISCUSSION

In this work, we report the two-step synthesis of compounds **9a**-**m** and **19a**-**d**, which contain three different heterocycles: pyridine, pyrrolidin-2-one, and 1*H*-1,2,3-triazole (4-substituted and 1,4-disubstituted) (**Scheme 3**). The use of orthogonal, bifunctional reagents plays a central role in the IMCR/post-transformation strategy, leading to the rapid generation of molecular complexity in both bis-heterocycles **6a**-**m** and final products **9a**-**l**. In the first step, the synthesis of **6a**-**m** occurs by a cascade process combining an Ugi-3CR with aza Diels-Alder, *N*-acylation, and aromatization reactions to give a complex terminal alkyne functionalized at the α-position with a fused bis-heterocycle. Two fused rings were created in the process, resulting in pyrrolo[3,4-*b*]pyridin-5-ones **6a**-**m**.

To optimize the cascade process, we attempted to synthesize complex alkyne **6a** by sequentially reacting propargylamine (**1**), benzaldehyde (**2a**), isocyanide **3a**, and maleic anhydride (**4**) using toluene (**Table 1**). Performing the reaction without catalyst at 60–80 °C under conventional conditions produced **6a** in 13% yield (entry 1, **Table 1**). When the reaction was carried out using catalytic amounts of NH_4Cl at 60–80 °C (Janvier et al., 2002), the product was isolated in 43% yield (entry 2, **Table 1**). Under microwave conditions, the yield increased to 57% (entry 3, **Table 1**). In previous reports, we used TsOH for the aromatization process after a Diels-Alder cycloaddition to construct the isoindolin-1-one moiety (Rentería-Gómez et al., 2016a). Unfortunately, bis-heterocycle **6a** was not detected when TsOH was used; only decomposition was observed by TLC.

TABLE 1 | IMCR based cascade strategy screening conditions.



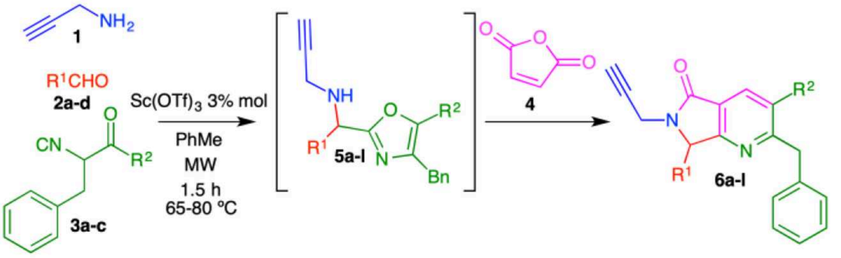
Entry^a	Solvent^b	Additive	T (°C)	t (h)	Yield (%)^g
1	PhMe	——-	65–80	12	13
2	PhMe	NH_4Cl^c	65–80	12	43
3	PhMe	NH_4Cl^c	65–80^d	1.5	57
4	PhMe	TsOH^e	65-80^d	1.5	—
5	PhMe	Sc(OTf)$_3$^{f}	65–80	12	42
6	**PhMe**	**Sc(OTf)$_3$^{f}**	**65–80^d**	**1.5**	**69**
7	PhMe	Yb(OTf)$_3$^{f}	65-80^d	1.5	62

[a] 1.0 equiv. **1**, 1.0 equiv. **2a**, 1.2 equiv. **3a**, 1.4 equiv. **4**.
[b] 1.0 mL solvent.
[c] 1.4 equiv.
[d] MW (100 W).
[e] 1.5 equiv.
[f] 3.0 mol%.
[g] isolated products.
Bold values indicate the best conditions.

Using catalytic Sc(OTf)$_3$ under conventional heating, **6a** was obtained in 42% yield (entry 5, **Table 1**). Microwave heating with Sc(OTf)$_3$ or Yb(OTf)$_3$ (Islas-Jácome et al., 2011, 2012) raised the yield to 69 and 62%, respectively (entries 6-7, **Table 1**). We therefore used the optimal conditions (entry 6: 3 mol% Sc(OTf)$_3$, microwave heating 60–80 °C, 1.5 h) to synthesize the series of fused bis-heterocycles **6a-l** (**Table 2**).

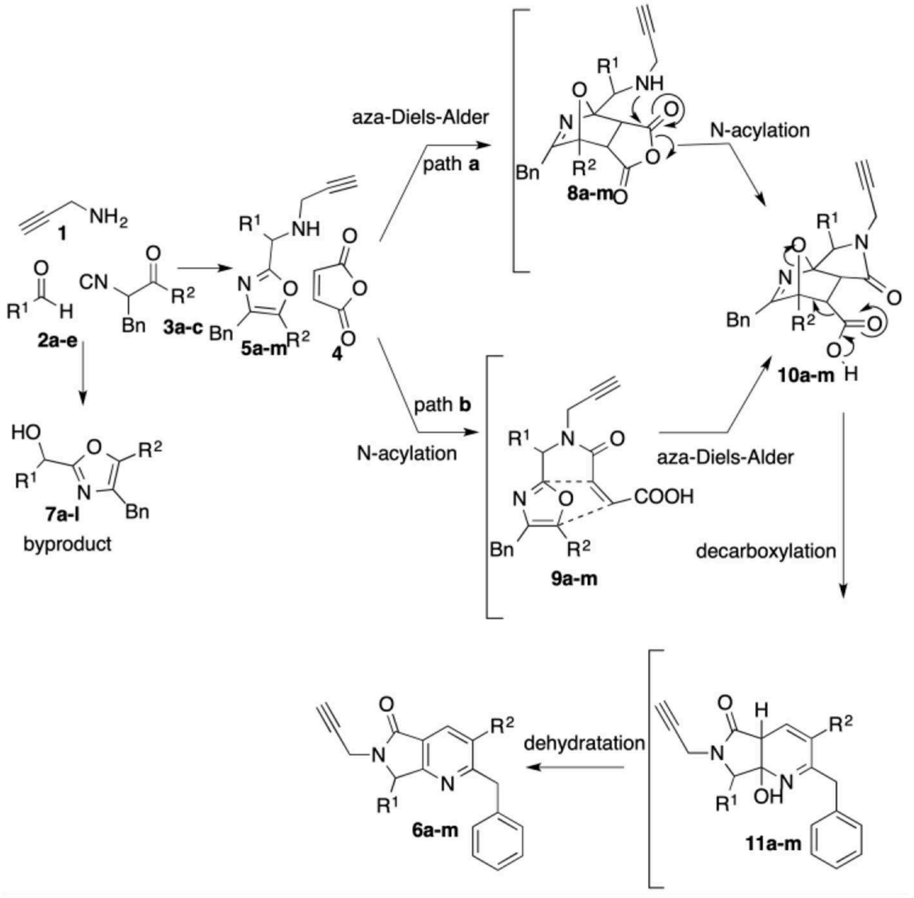
The scope of this cascade process was explored using alkyl and aryl aldehydes **2a-d** and amide-containing isocyanides **3a-c** (**Table 2**). The role of fluorine atoms in improving bioavailability, lipophilicity and metabolic resistance in bioactive molecules is well-documented (Purser et al., 2008). The products **6c**, **6g**, and **6k** containing fluorine atom was synthesized. Piperidine, morpholine, and diethylamine were incorporated as substituents of isocyanides **3a-c**. These fragments can act as structural bioisosteres, preferably interacting with some amino acids

TABLE 2 | Synthesis of the 6-propargyl-pyrrolo[3,4-*b*]pyridin-5-ones **5a-l**.



Product^a	R^1	R^2	Yield (%)^b
6a	Ph	piperidine	64
6b	3,4-diOMePh	piperidine	72
6c	4-FPh	piperidine	62
6d	*n*-hexyl	piperidine	64
6e	Ph	morpholine	69
6f	3,4-diOMePh	morpholine	66
6g	4-FPh	morpholine	66
6h	*n*-hexyl	morpholine	67
6i	Ph	diethylamine	59
6j	3,4-diOMePh	diethylamine	63
6k	4-FPh	diethylamine	64
6l	*n*-hexyl	diethylamine	66

[a] Reactions performed with 1.0 equiv. propargylamine (**1**), 1.0 equiv. aldehyde **2a-d**, 1.2 equiv. isocyanide **3a-c**, 1.4 equiv. maleic anhydride (**4**), 3 mol% Sc(OTf)$_3$, 1 mL PhMe.
[b] isolated products.



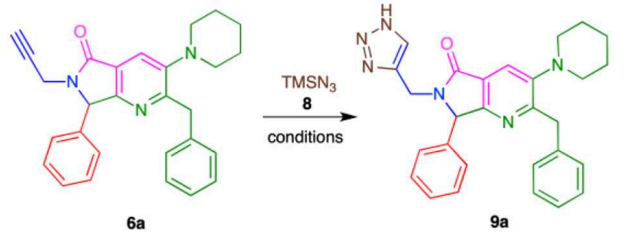
SCHEME 4 | Plausible reaction mechanism.

allowing in some cases improve biological activity (Kalinsky and Weinstein, 1954; Sander et al., 2008; Meng et al., 2011; El-Nassan, 2015; Yu et al., 2015; Sato et al., 2017).

The highest yield (72%) was obtained for product **6b**, which contains 2,3-dimethoxyphenyl and piperidine as substituents at R^1 and R^2, respectively. Contrarily, bis-heterocycle **6i**, with phenyl and diethylamine substituents, was obtained in the lowest yield (59%). In fact, among all products, the diethylamine-containing analogs **6i**-**l** were synthesized in lower yields, which can be attributed to the lower stability of this isocyanide in acidic media. In all cases, the primary byproducts were the corresponding 5-aminooxazoles resulting from Lewis-acid-catalyzed chain-ring tautomerization of the isocyanides **3a**-**c** (Gao et al., 2016). Consistent with reports by Zhu (Cuny et al., 2004; Wang et al., 2007), we also observed, as minor byproducts, the alcohols resulting from isocyanide addition to the aldehydes prior to oxazole formation (**7**) (**Scheme 4**). The plausible reaction mechanism for the formation of pyrrolo[3,4-*b*]pyridin-5-ones **6a**-**l** is supported by computational calculations performed previously using DFT methods (**Scheme 4**) (Islas-Jácome et al., 2016).

Conditions were screened for the [3+2] cycloaddition using terminal alkyne **6a** (**Table 3**). Heating at 100 °C for 12 h with 1.0 equiv. $TMSN_3$ and 3 mol% CuI provided tris-heterocycle **9a** in a modest 48% yield (entry 1, **Table 2**). Increasing the equivalents of the volatile $TMSN_3$ to 1.5 or 2.0 raised the

TABLE 3 | Screening conditions for the [3+2] cycloaddition.

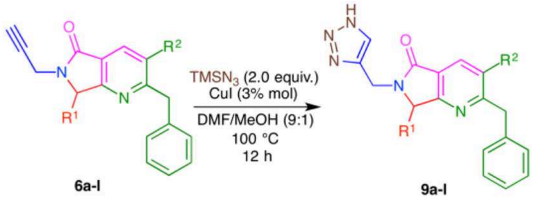


Entry	$TMSN_3$ (equiv.)	CuI (mol%)	T (°C)	t (h)	Yield (%)[a]
1	1.0	3	100	12	48
2	1.5	3	100	12	69
3	**2.0**	**3**	**100**	**12**	**77**
4	2.0	5	100	18	75
5	2.0	3	100[b]	0.5	52

[a] *isolated products.*
[b] *MW (100 W).*
Bold values indicate the best conditions.

yield of **9a** to 69 and 77%, respectively (entries 2-3, **Table 2**). Using additional CuI (5% mol) and increasing the reaction time to 18 h did not improve the yield (entry 4, **Table 2**). Microwave heating reduced both the reaction time and the yield to 52%, as high amounts of byproducts were detected (entry 5, **Table 2**).

TABLE 4 | Synthesis of 4-substituted 1*H*-1,2,3-triazoles **9a-l**.

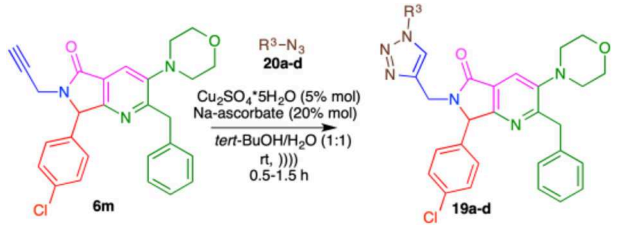


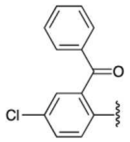
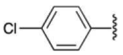
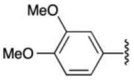
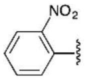
Product^a	R^1	R^2	Yield (%)^b
9a	Ph	piperidine	77
9b	3,4-diOMePh	piperidine	75
9c	4-FPh	piperidine	80
9d	*n*-hexyl	piperidine	70
9e	Ph	morpholine	63
9f	3,4-diOMePh	morpholine	73
9g	4-FPh	morpholine	80
9h	*n*-hexyl	morpholine	75
9i	Ph	diethylamine	73
9j	3,4-diOMePh	diethylamine	70
9k	4-FPh	diethylamine	78
9l	*n*-hexyl	diethylamine	75

[a] *1.0 equiv. alkyne **6a-l**, 2.0 equiv. TMSN$_3$, 3% mol CuI in MeOH/DMF (9:1 v/v, 0.5 M) at 100 °C for 12 h.*

[b] *isolated products.*

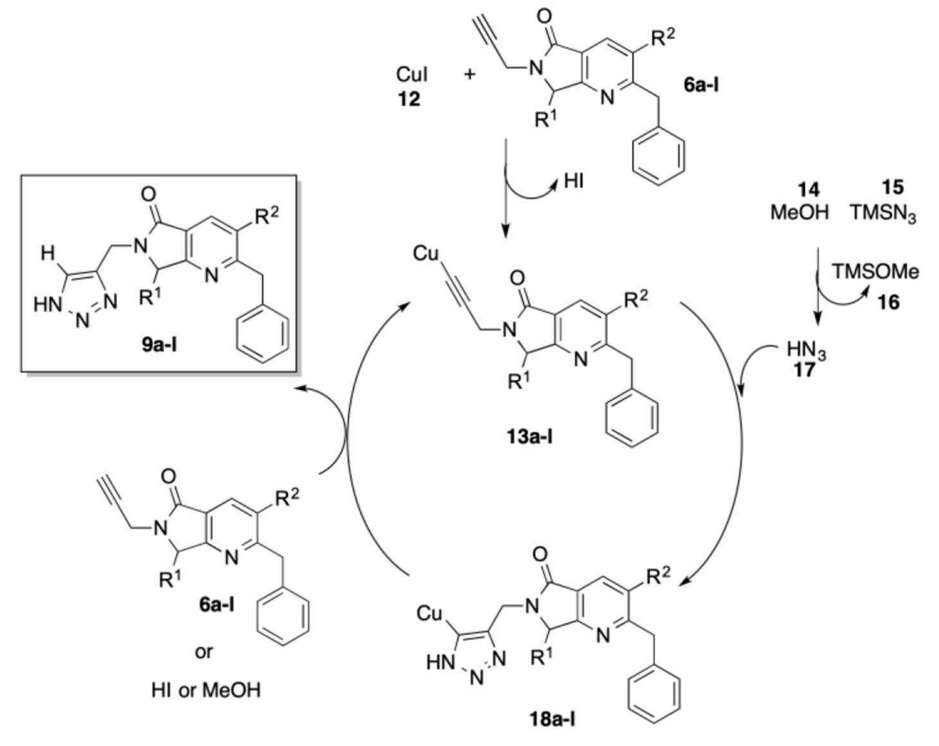
TABLE 5 | Synthesis of 1,4-disubstituted 1*H*-1,2,3-triazoles **19a-e**.



Product^a	R^3	t (min)	Yield (%)^b
19a		90	83
19b		30	89
19c		45	93
19d		45	90

[a] *1.0 equiv. azide **20a-e**, 5% mol Cu$_2$SO$_4^*$5H$_2$O, 20% mol Na-ascorbate in H$_2$O/tert-BuOH (1:1 v/v, 0.3 M) at rt (USI) for 30-90 min.*

[b] *isolated products.*



SCHEME 5 | Plausible CuAAC reaction mechanism.

Using the optimized conditions, a series of tris-heterocycles (**9a**-**l**) was synthesized from complex alkynes **6a**-**I** via the [3+2] cycloaddition in good yields (70–80%, **Table 4**). The highest yields were obtained for the 4-fluorophenyl analogs. Alkynes **6a**-**l** and triazole products **9a**-**l** were fully characterized by IR, ^{1}H and ^{13}C NMR, and HRMS (see the **Supplementary Material** for further details). Several attempts to obtain adequate crystals for X-ray analysis were performed without success.

In **Scheme 5**, we show a plausible reaction mechanism for the alkyne-azide [3+2] cycloaddition to produce 4-substituted 1*H*-1,2,3-triazoles. The reaction likely proceeds through the formation of copper acetylide species **13a**-**l** from terminal alkynes **6a**-**l** with CuI (**12**) and *in situ* generation of HN_3 (**17**) from the reaction of $TMSN_3$ (**15**) and MeOH (**14**). Copper-assisted cycloaddition between **13a**-**l** and HN_3 (**17**) takes place to form intermediates **18a**-**l**. Protonolysis of the C-Cu bond of **18a**-**l** by terminal alkynes **6a**-**l**, HI, or MeOH affords 4-substituted 1*H*-1,2,3-triazoles **9a**-**l** (Jin et al., 2004).

Having the methodology for the synthesis of compounds **9a**-**l**, we next explored the scope of use de terminal alkynes linked to bis-heterocycles using organic azides to obtain the 1,4-disubstituted 1,2,3-triazoles (**19a**-**d**) via CuAAC. Compound **6m** was synthetized (60% yield) and selected as model. Phenyl azides with different stereo-electronic natures (**20a**-**d**) were prepared from aromatic amines via diazotization with sodium nitrite in water in the presence of p-TsOH followed by reaction with sodium azide at room temperature (Kutonova et al., 2013).

First, the reaction was carried out under constant stirring, at room temperature, using **6m** and azide **20a** obtaining an 85% yield of 1,4-disubstituted 1,2,3-triazole **19a** after 5 h. When the reaction was carried out using ultrasound-assisted irradiation (USI) at room temperature, the product **19a** was obtained in 1.5 h, with a yield of 83%. For this reason, we decided to use the USI protocol for the synthesis of 1,4-disubstituted 1-*H*-1,2,3-triazoles (**19a**-**d**). The reactions under USI resulted in reduced reaction times (30–90 min) and good yields (83–93%) in the CuAAC for the synthesis of **19a**-**e** (**Table 5**).

CONCLUSIONS

We have developed a new and efficient strategy to synthesize 4-substituted and 1,4-disubstituted 1*H*-1,2,3-triazoles linked to pyrrolo[3,4-*b*]pyridin-5-ones. Molecules containing these heterocycles together are novel. The molecules synthesized contain privileged tris-heterocycles which could have applications in medicinal chemistry and coordination chemistry.

The IMCR based cascade process coupled with CuAAC strategy, as convergent and powerful tool toward the synthesis of bis and tris heterocycles is unreported.

DATA AVAILABILITY

All datasets generated for this study are included in the manuscript and/or the **Supplementary Files**.

AUTHOR CONTRIBUTIONS

MR-G, RG-M, and DV have made a substantial, direct and intellectual contribution to the work. SP was responsible for performing the initial experiments. AI-J was responsible for designing and analyzing the results. All authors discussed the whole project, wrote the publication, and approved it for publication.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fchem.2019.00546/full#supplementary-material

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A One-Pot Synthesis of Oxazepine-Quinazolinone bis-Heterocyclic Scaffolds via Isocyanide-Based Three-Component Reactions

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A novel, efficient and environmentally friendly approach has been developed for the synthesis of biologically important *bis*-heterocyclic oxazepine-quinazolinone derivatives. The structurally interesting compounds of high purity were synthesized by a one-pot three-component reaction of 2-(2-formylphenoxy) acetic acid and 2-aminobenzamide as bifunctional reagents and an isocyanide without using any catalyst, with excellent overall yields.

Keywords: oxazepine, quinazolinone, Ugi reaction, multicomponent reaction, isocyanide

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INTRODUCTION

To date, the development of new methods for the synthesis of heterocyclic compounds has been and remains a hot topic in organic chemistry, due to their importance in biologically active natural products and synthetic materials (Armstrong and Collins, 2010; Kaur et al., 2016). Remarkably, seven out of the top ten pharmaceutical products according to worldwide sales in 2009 contain a heterocyclic motif as their core structure (Chen et al., 2014). Seven-membered heterocyclic rings have been the object of deep investigation owing to their prevalence in molecules with biological activities (Goutham et al., 2015; Voigt et al., 2015; Xu, 2016).

Oxazepines, a privileged scaffold in medicinal chemistry, are a well-known class of seven-membered heterocycles with two heteroatoms and have been receiving continuing attention due to the wide range of biological activities. Among these activities, it is worth mentioning anti-inflammatory (Chakrabarti and Hicks, 1987; Verma et al., 2008), antifungal (Serrano-Wu et al., 2002), antithrombotic (Mishra et al., 2010; Agirbas et al., 2011), anti-epileptic (Pekcec et al., 2009), anti-convulsant (Sharma et al., 2008), progesterone agonist (Dols et al., 2008), antagonist and analgesic (Hallinan et al., 1994), anti-histaminic (Sleevi et al., 1991), anti-psychotic (Liegeois et al., 1994; Liao et al., 1999), anxiolytics (Effland et al., 1982), anti-aggregating (Aono et al., 1991), and epidermal growth factor receptor (EGFR) tyrosine kinase inhibitory (Smith et al., 2006) activities. Compounds containing oxazepine motif, sintamil (Nagarajan et al., 1986) and loxapine (Liao et al., 1999) were reported, due to their antidepressant and potential clozapine-like properties, respectively (**Figure 1**) (Samet et al., 2005; Liu et al., 2011) Considering the structural characteristics of the benzoxazepine-3-ones, the existence of seven-membered heterocyclic ring system, fused aromatic group and the group –N–C(=O)–, similar to protein amide bond, it is reasonable to expect inherent physiological activities (Agirbas et al., 2011).

Nitrogen heterocycles are the most important structural units in natural products and synthetic drugs. Thus, tremendous efforts have been made to develop new strategies and technologies for their synthesis (Tietze, 1996; Tietze and Modi, 2000; D'Souza and Mueller, 2007; Priebbenow et al., 2011; Rixson et al., 2012). Typically, quinazolinone derivatives widely occur in natural products (Yoshida et al., 1991; Wattanapiromsakul et al., 2003), and they show various biological and pharmacological activities, such as anti-inflammatory, antioxidant, antimicrobial, antipsychotic, and antihypertensive activity, strong analgesic activity, and many effects on the central nervous system (CNS) (Khalil et al., 1994; Bartoli et al., 1998; Liverton et al., 1998; Malecki et al., 2004; Arora et al., 2011; Chawla and Batra, 2013; Nepali et al., 2013). A quinazolinone motif is present in the structure of numerous drugs, e.g., the hypnotic methaqualone, the muscle relaxant afloqualone, the diuretic quinethazone, the antineoplastic agents trimetrexate and raltitrexed, and the serotonin antagonist ketanserin (**Figure 2**) (Kleemann et al., 1999; Abraham, 2003).

RESULTS AND DISCUSSION

Combination of a molecule with several heterocyclic compounds with different pharmacological activities due to the synergism effect is a useful strategy to assign and discover new biological compounds. The Ugi four-component reaction (U-4CR) is one of the most commonly used multicomponent reactions (MCRs), in which a carboxylic acid, an amine, a carbonyl compound, and an isocyanide are reacting to result in peptide-like heterocyclic products (Hebach and Kazmaier, 2003; Dömling, 2006; Giovenzana et al., 2006; Ngouansavanh and Zhu, 2007; Hartweg and Becer, 2016; Yugandhar et al., 2016). Although a large diversity can be quickly achieved through the U-4CR, the scaffolds that are accessible through it are limited. The replacement of two participants in this reaction with a single bifunctional reagent is a fruitful strategy to broaden the scope of structures that are accessible by the U-4CR and toward various drug-like heterocycles (Hulme and Dietrich, 2009). 2-(2-formylphenoxy) acetic acid **1** has previously been employed to provide various derivatives of oxazepines (Zhang et al., 1999; Ilyin et al., 2006; Tsaloev et al., 2011; Hajishaabanha and Shaabani, 2014). As a part of our ongoing research program on the isocyanide-based MCRs (Shaabani et al., 2007, 2008a,b, 2009, 2011, 2014, 2016; Hajishaabanha and Shaabani, 2014), a novel strategy was designed to explore the Ugi one-pot three-component four-center reaction with two bifunctional starting materials, 2-(2-formylphenoxy)acetic acid **1** and 2-aminobenzamide **2** for the synthesis of *bis*-heterocyclic oxazepine-benzodiazepine **4** (**Scheme 1**, cyclization path A) or oxazepine-quinazolinone **5** (**Scheme 1**, cyclization path B) derivatives. The results show the reaction proceeded *via* the pathway B affording a new interesting class of oxazepine-quinazolinone **5** in high yields.

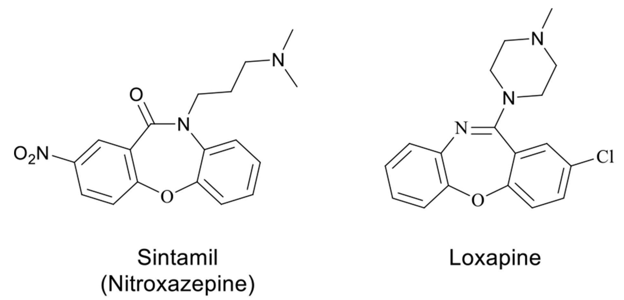


FIGURE 1 | Examples of some biologically important oxazepines.

In a pilot experiment, 2-(2-formylphenoxy)acetic acid **1**, 2-aminobenzamide **2**, and *tert*-butyl isocyanide **3a** were refluxed in ethanol. The progress of reaction was monitored by TLC. After 24 h, the reaction was completed and *N*-(*tert*-butyl)-5-oxo-5,7-dihydro-13*H*-benzo[6,7][1,4] oxazepino[4,3-a]quinazoline-13-carboxamide **5a** (**Scheme 1**, cyclization path B) was obtained in 94% yield (**Scheme 2**). It is worth mentioning that in the course of this reaction, one C-C bond, several C-N bonds, one amide group, a benzoxazepine ring and a quinazolinone ring are newly

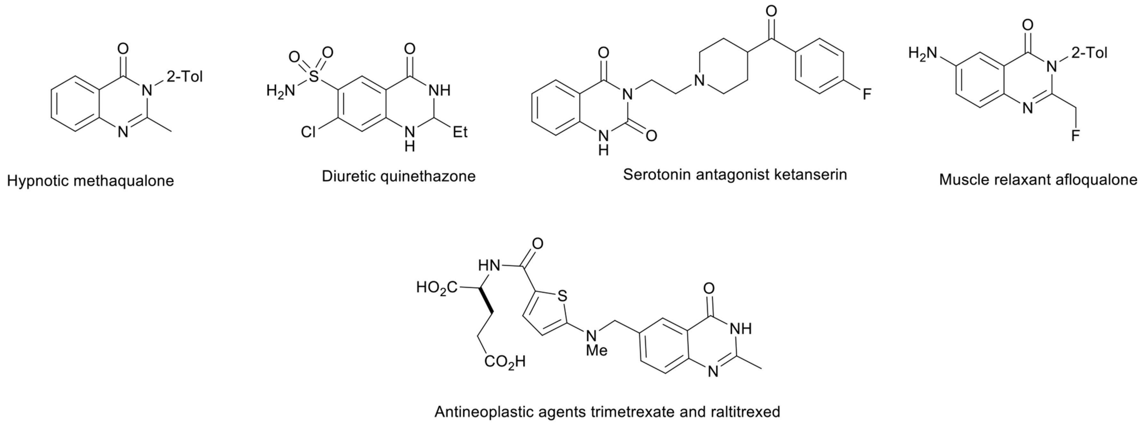
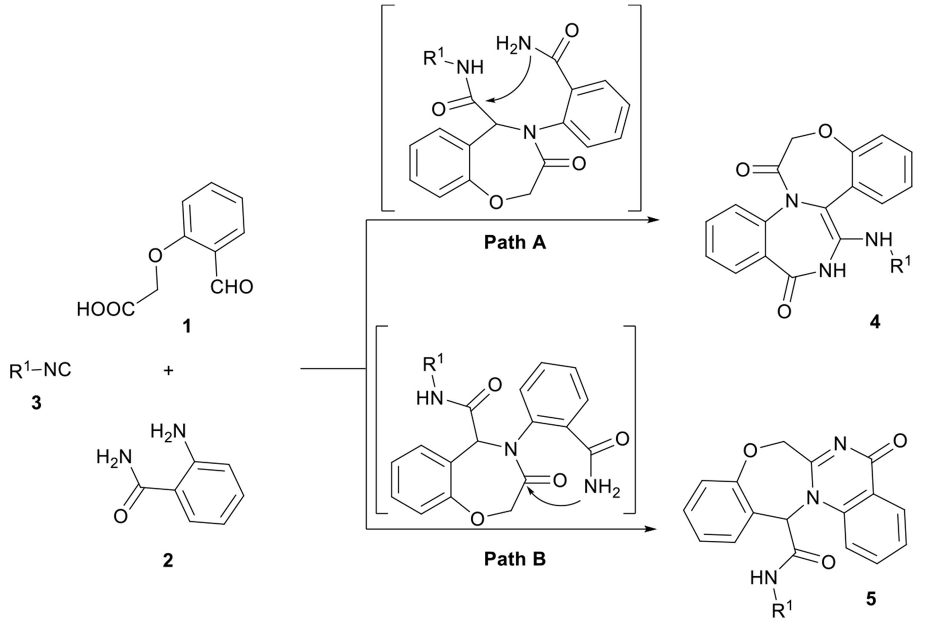
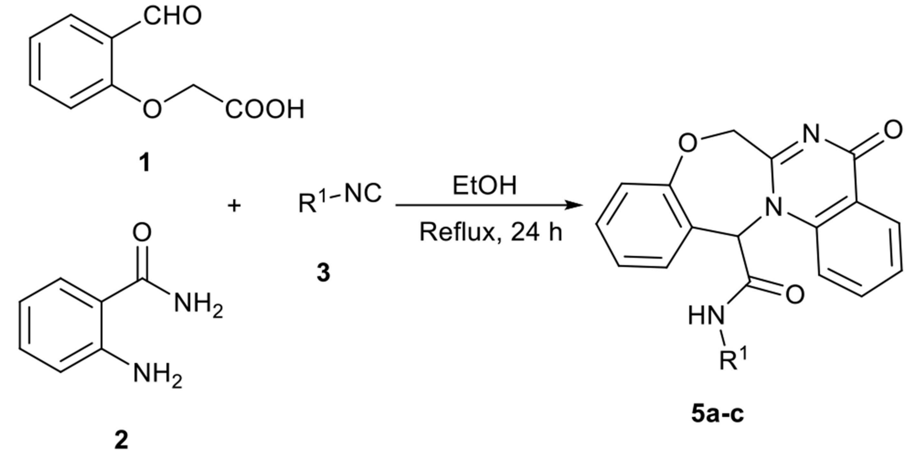


FIGURE 2 | Structures of some quinazolinone derivative drugs.

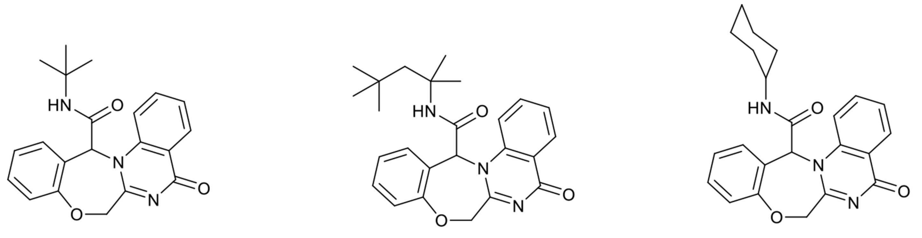


SCHEME 1 | Intramolecular cyclization of Ugi product.



R^1=(a) tert-butyl, (b) 1,1,3,3-tetramethylbutyl or (c) cyclohexyl

SCHEME 2 | Synthesis of oxazepine-quinazolinone *bis*-heterocyclic scaffolds **5**.



5a (94%) **5b** (98%) **5c** (91%)

FIGURE 3 | Structure and isolated yields of products **5**.

formed. These new structures broaden the scaffolds that are accessible through Ugi reaction and may represent interesting pharmacophores.

In view of the success of the above reaction, we explored its scope and limitations, by extending the procedure to various isocyanides **3a-c**. As indicated in **Figure 3**, the reactions proceed very efficiently in EtOH and led to the formation of novel oxazepine-quinazolinone *bis*-heterocyclic scaffolds **5a-c** in excellent yields. The reaction did not require any optimization.

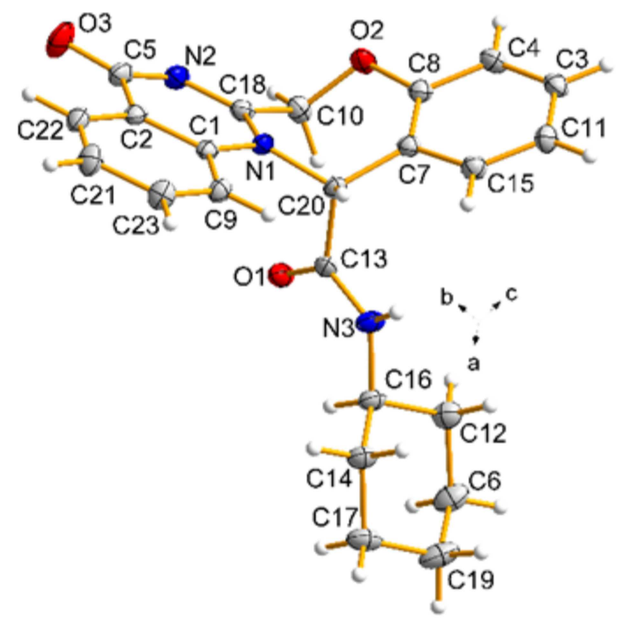
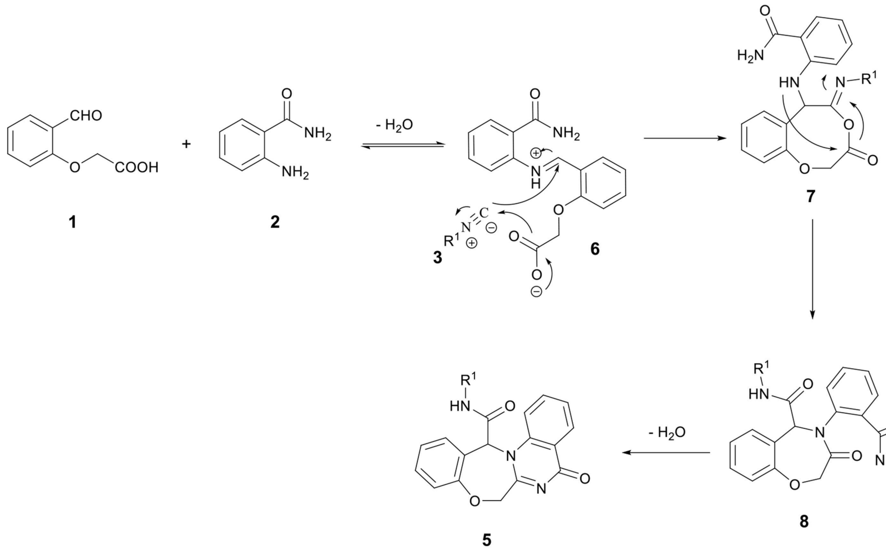


FIGURE 4 | ORTEP diagram for **5c**.

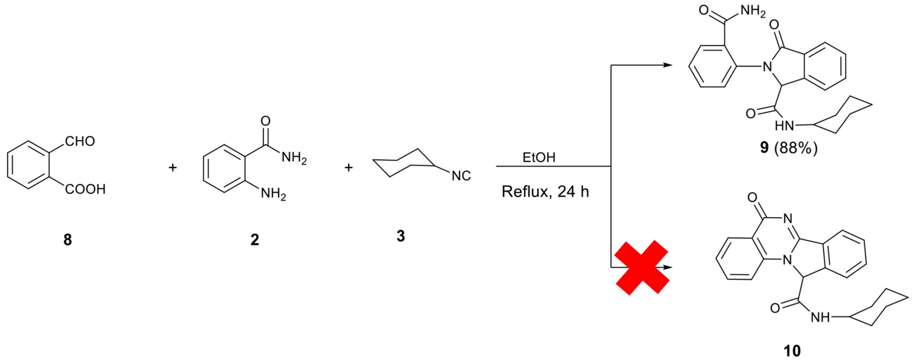
The structures of products **5** were deduced from their IR, ^{1}H NMR, ^{13}C NMR, mass spectra and CHN analysis data. The ^{1}H NMR spectrum of **5c** consisted of a multiplet for the methylene protons of the cyclohexyl ring (δ =1.03-1.63 ppm, 10H), a broad singlet for the NH–C*H* cyclohexyl (δ = 3.58 ppm, 1H), two doublets for two non-equivalent methylene protons of the oxazepine ring (δ = 4.83 and 5.37 ppm, J = 14.5 Hz), a singlet for CH (δ = 6.65 ppm, 1H), a multiplet for aromatic protons and NH (7.03–8.11 ppm, 9H). Also, the ^{1}H decoupled ^{13}C NMR spectrum of **5c** is completely consistent with the suggested structure. The mass spectra of these compounds displayed molecular ion peaks at the appropriate *m/z* values. Finally, the structure of the product **5c** was confirmed unambiguously by single-crystal X-ray analysis (**Figure 4**) (Petříček et al., 2014).

A possible mechanism for the formation of products **5** is shown in **Scheme 3**. It is conceivable that the initial event in this reaction is the nucleophilic attack of amine **2** to formyl group to afford the iminium intermediate **6**. The addition of the carbenoid C-atom of the isocyanides **3** onto the iminium group followed by the addition of the carboxylate ion onto the C-atom of the nitrilium ion leads to the formation of the adduct **7**, which undergoes an intramolecular acylation known as Mumm rearrangement to give the Ugi adduct **8**. Finally, Ugi adduct **8** undergoes an amide-amide cyclocondensation through pathway A (instead of pathway B) to give the oxazepine-quinazolinone *bis*-heterocyclic products **5** (**Scheme 3**).

It is worth mentioning that to expand the structure diversity accessible through this type of Ugi 3-component reaction, the reaction between 2-formylbenzoic acid **8**, 2-aminobenzamide **2**, and cyclohexyl isocyanide under the previously mentioned conditions was also investigated. However, Ugi adduct **9** does not undergo an intramolecular cyclization to give the expected quinazolinone-isoindoline *bis*-heterocyclic product **10**.



SCHEME 3 | Proposed mechanism for the formation of products **5**.



SCHEME 4 | 2-Formylbenzoic acid in Ugi 3-component reaction.

The analytical data obtained on the final material support the preparation and isolation of **9** as the product (**Scheme 4**).

The fused benzodiazepine-quinazolinone is a unique tetracyclic scaffold in several respects. A SciFinder and ChEMBL database search revealed no other example (**Figure S1**). Known substructures are benzoxazepines and quinazolinones. The parent scaffold benzoxazepine-quinazolinone is non planar through the introduction of the seven-membered aliphatic oxazepine ring in the center of the tetracycle, comprising a butterfly shape and showing an interesting combination of pharmacophores (**Figure 5**). The quinazolinone bicycle and the phenyl group are planar and can potentially undergo pi stacking interactions with the receptor amino acids. The quinazolinone also comprise a rare vicinal hydrogen bond acceptor hydrogen bond acceptor moiety. The other nitrogen atom is fully encapsulated in the ring systems and involved in the aromatic bicycle and cannot undergo hydrogen bonding interactions. The ether oxygen of the seven-membered oxazepane ring can act as another hydrogen bond acceptor.

A randomly generated library of benzoxazepine-quinazolinones reveals a good fraction of compounds with an attractive MW and cLogP thus rendering the scaffold interesting for receptor ligand interactions (**Figure 5** and **Supplementary Information**).

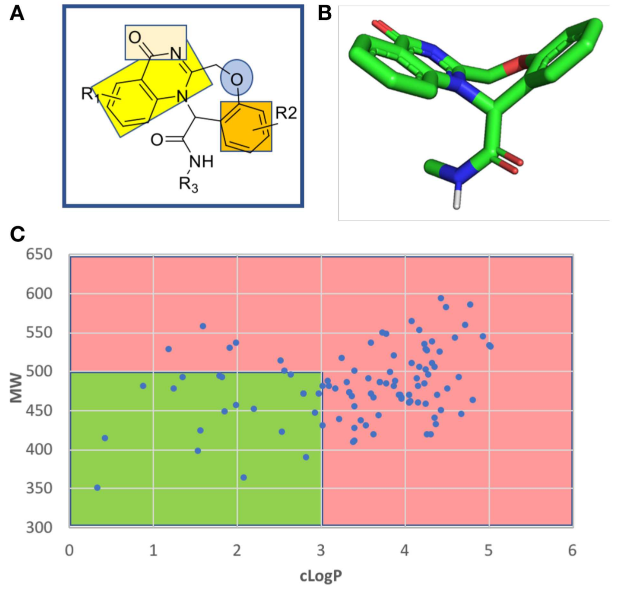


FIGURE 5 | Chemoinformatic analysis of the unprecedented benzoxazepine-quinazolinone scaffold. **(A)** 2D structure and pharmacophores. **(B)** 3D energy minimized butterfly structure of the scaffold induced by the central seven-membered oxazepine ring. **(C)** Molecular weight over lipophilicity of a randomly generated a 100 compound library highlighting the drug-like preferred and non-preferred area in green and red, respectively.

CONCLUSION

In conclusion, we have successfully developed a one-pot three-component four-center reaction strategy leading to novel *bis*-heterocyclic oxazepine-quinazolinones which are two important pharmacological and biological scaffolds, starting from simple and readily available inputs. To the best of our knowledge, it is the first report of using two bifunctional starting materials in Ugi reaction to obtain fused oxazepine-quinazolinone heterocycles. Moreover, it is a new isocyanide based bicyclization reaction (Gao et al., 2015, 2016; Hao et al., 2016; Tang et al., 2016). The reaction is high-yielding and product isolation is very straightforward. Moreover, it is noteworthy that this operationally friendly and scalable manner allows C–C bond, C-O and C–N bond formation with excellent scope. The potential uses of this route in synthetic and medicinal chemistry may be significant, since the products share structural and functional group properties of the biologically active molecules. Structural diversity and biological activity of the synthesized compounds will be tested and results of these tests will be reported in due course.

DATA AVAILABILITY

All datasets generated for this study are included in the manuscript and/or the **Supplementary Files**.

AUTHOR CONTRIBUTIONS

SS did the design, synthesis, and wrote the manuscript. AS directed the project and co-wrote the manuscript. MK and MD did the crystallographic part.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fchem.2019.00623/full#supplementary-material

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Unimolecular Exciplexes by Ugi Four-Component Reaction

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Exciplex or excited complex emission is an excited state process, arising from considerable charge transfer of an excited energy donor to an acceptor, which can be identified by the occurrence of a redshifted emission band that is absent in the individual constituents. Particularly interesting are exciplexes that are formed by intramolecular excited state interaction, which are inherently concentration independent. Based upon our previous experience in the Ugi-4CR syntheses of donor-acceptor conjugates capable of photo-induced intramolecular electron transfer (PIET), that is, generation of light-induced charge separation, we now disclose the diversity-oriented approach on unimolecular exciplex emitters and their reference systems by Ugi-4CR. The photophysics is studied by absorption and emission spectroscopy and accompanied by density functional theory (DFT) and time-dependent density functional theory (TDDFT) calculations.

Keywords: absorption, bichromophores, DFT, emission, energy transfer (ET) dyes, exciplexes, isonitrile, multicomponent reaction

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INTRODUCTION

Molecular luminescence (Lakowicz, 2006; Valeur and Berberan-Santos, 2012) is a widespread phenomenon of functional organic materials (Müller and Bunz, 2007) and finds broad application in many fields of science and technology, ranging from fundamental science (luminescence spectroscopy) (Wolfbeis, 1993; Valeur and Brochon, 2012) over biophysical analytics (Chen et al., 1998; Nilsson et al., 2002; Wagenknecht, 2008; Demchenko et al., 2009; Kim and Park, 2009; Cairo et al., 2010), diagnostics (Kobayashi et al., 2010; Carter et al., 2014), and dye lasers (Thiel, 2000; Shankarling and Jarag, 2010) to sensors (Loving et al., 2010; Klymchenko, 2017; Zhang et al., 2017) and organic light-emitting diodes (OLED) (Müllen and Scherf, 2006; Park et al., 2011; Thejo Kalayani and Dhoble, 2012; Li, 2015). Besides fluorescence and phosphorescence as radiative deactivation of electronically excited singlet or triplet states, also radiative states arising from inter- or intramolecular electronic interaction, eventually by energy or electron transfer, are particularly interesting. With this respect, exciplexes (excited complexes) and excimers (excited dimers) are emissive charge-transfer complexes, which are formed by excitation of one of the constituting chromophores that in turn collides with a second chromophore in its electronic ground state (Balzani et al., 2003; Balzani, 2008). In contrast to charge-separated charge transfer states, exciplexes and excimers can deactivate by broad structureless emission (Lakowicz, 2006; Valeur and Berberan-Santos, 2012), however, redshifted with respect to the constituting individual chromophores (**Figure 1**) (Balzani et al., 2003; Balzani, 2008). While excimers constitute from identical chromophores in exciplexes, the two colliding chromophores differ in their structure and nature. In either case, stability results from Coulomb and favorable orbital interactions at distances between 3 and 4 Å.

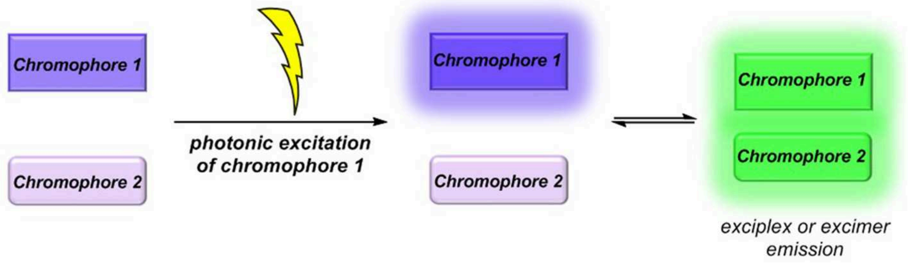


FIGURE 1 | Exciplex or excimer emission as a radiative quenching pathway by intermolecular chromophore-chromophore interaction in the excited state.

Since exciplex emission represents a pathway of quenching the excited molecule's fluorescence, this phenomenon might be employed for sensing proximity of two interacting chromophores by a radiative process. This excited state phenomenon is particularly interesting—absorption spectra are simple superpositions of their constituting chromophores—as the emission will be dependent on the solvent polarity in terms of energy of the exciplex state as well as in terms of the intensity (Kavarnos, 1993).

If two chromophores are placed into a unimolecular setting, that is, by covalent ligation, the unimolecular exciplex emission is inherently independent of concentration and diffusion control, in contrast to exciplex emission arising from two particles. The positive solvatochromicity of the exciplex emission band, that is, a redshift of the longest wavelength emission band with increasing solvent polarity, as well as its decreasing effect on the fluorescence quantum yield and fluorescence lifetimes has impressively been shown for ether-tethered dyads consisting of pyrene and 2-benzylidenemalononitrile as constituting chromophores (Piuzzi, 1993; Zhang et al., 1997; Piuzzi et al., 1999). Likewise, alkyl-tethered pyrene/anthracene-*N,N*-dimethylaniline dyads were studied in detail by time-resolved laser spectroscopy (Mataga and Miyasaka, 1999). In hexane, the formation of the compact exciplex, where the hydrocarbon and the *N,N*-dimethylaniline moieties are sandwiched, occurs in the nanosecond time regime, while in acetonitrile, the loose exciplex forms within picoseconds after excitation, obviously due to a facilitated charge-transfer proceeding without conformational changes. Time-resolved transient absorption spectroscopy moreover supports that the compact exciplex bands are strongly broadened in contrast to the acetonitrile spectra, which clearly support the well-resolved signature of superimposing radical ion spectra, that is, a strong ion pair character. Intermediate solvent polarities account for signal broadening, that is, the population of more ordered compacted conformations.

As part of our program to methodologically develop concise syntheses of functional chromophores by multicomponent reactions (MCR) (Levi and Müller, 2016a), we are particularly interested in MCR syntheses of fluorophores (Levi and Müller, 2016b; Riva et al., 2016; Merkt and Müller, 2018; Müller, 2018) and donor-acceptor systems that interact in the excited state *via* photo-induced electron transfer (PIET) (Kavarnos, 1993; Lemmetyinen et al., 2011; Wenger, 2011; Ricks et al., 2012; Vauthey, 2012), as shown by non-radiative fluorescence quenching (Bucci and Müller, 2006; Bay et al., 2013, 2014; Bay and Müller, 2014). This can be considered as chromophore-chromophore interactions at short distances, that is, between Dexter and Förster radii.

Conceptually, we reasoned that employing a scaffold-forming MCR approach (Levi and Müller, 2016a) to exciplex-forming bichromophores could establish a concise general synthetic approach to these types of unimolecular exciplex emitters (**Figure 2**). In addition, if emission of non-interacting and exciplex conformers occurs simultaneously from this Boltzmann distribution, dual emission may arise, furnishing emission color mixing. Here, we report the Ugi-4CR synthesis of several representative unimolecular exciplex emitters consisting of an *N,N*-dimethyl aniline moiety as a donor and anthracene, naphthalene, or pyrene as acceptor chromophores, as well as reference chromophores. Furthermore, the absorption and emission spectroscopic characteristics are reported and discussed in the light of DFT and TDDFT calculations of the donor-acceptor systems.

RESULTS AND DISCUSSION

Synthesis

The Ugi four-component reaction (4CR) (Dömling and Ugi, 2000; Dömling, 2006; Biggs-Houck et al., 2010) generates the chemically robust α-aminoacyl amide scaffold with a high level of diversity and has widely and successfully been applied in biological and medicinal chemistry (Dömling et al., 2012). Encouraged by Ugi 4CR syntheses of a phenothiazine-anthraquinone-based PIET system and related dyads (Bay et al., 2013, 2014; Bay and Müller, 2014), characterized by cyclic voltammetry, steady-state UV/vis, and fluorescence spectroscopy, as well as femtosecond transient absorption spectroscopy for identification of the desired charge separated state after light excitation, we decided to transpose the Ugi 4CR to a novel synthesis of *N,N*-dimethylaniline-anthracene dyads, which are known to form exciplex emitters (Hui and Ware, 1976).

Methanol as a solvent is often most ideal for Ugi 4CR, however, portions of dichloromethane were found to beneficially increase the solubility and to ensure a homogeneous solution. In a model reaction employing 9-aminomethylanthracene

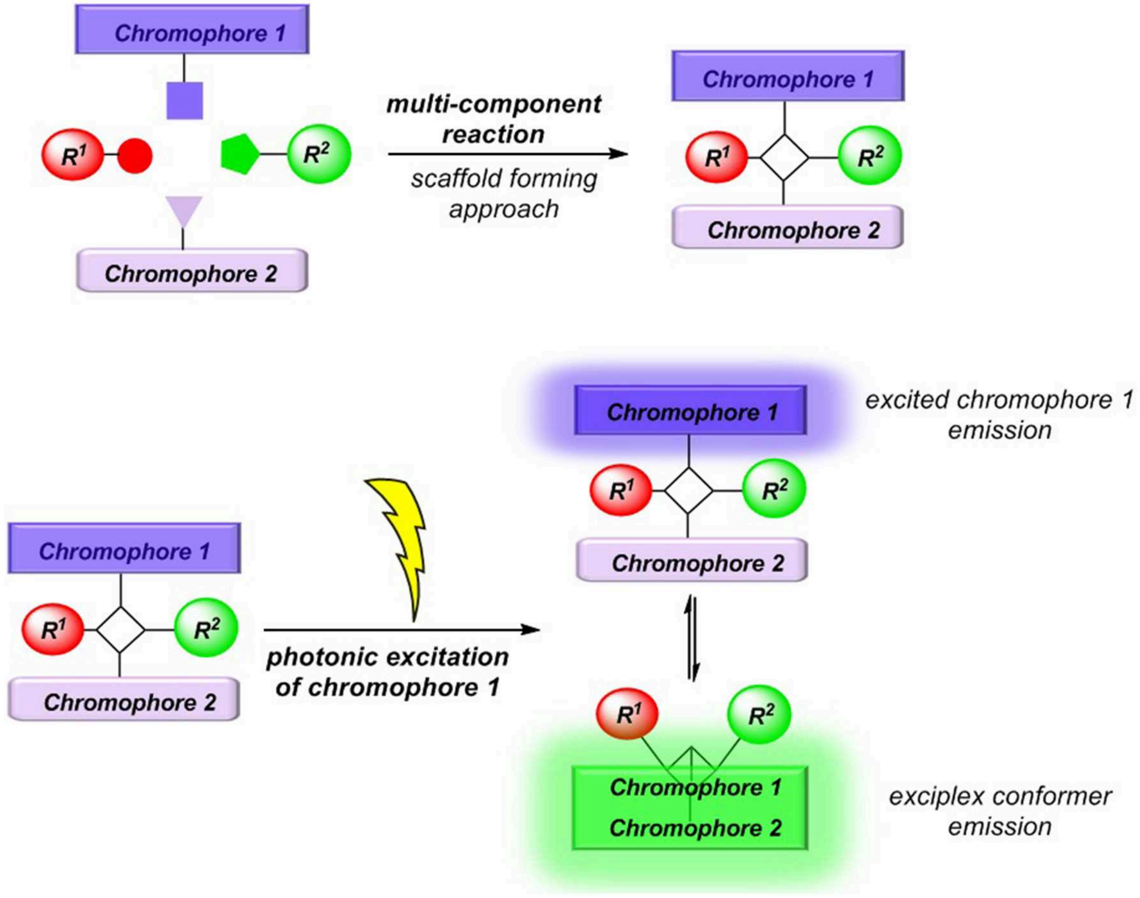


FIGURE 2 | MCR synthesis (scaffold-forming approach) of exciplex forming bichromophores.

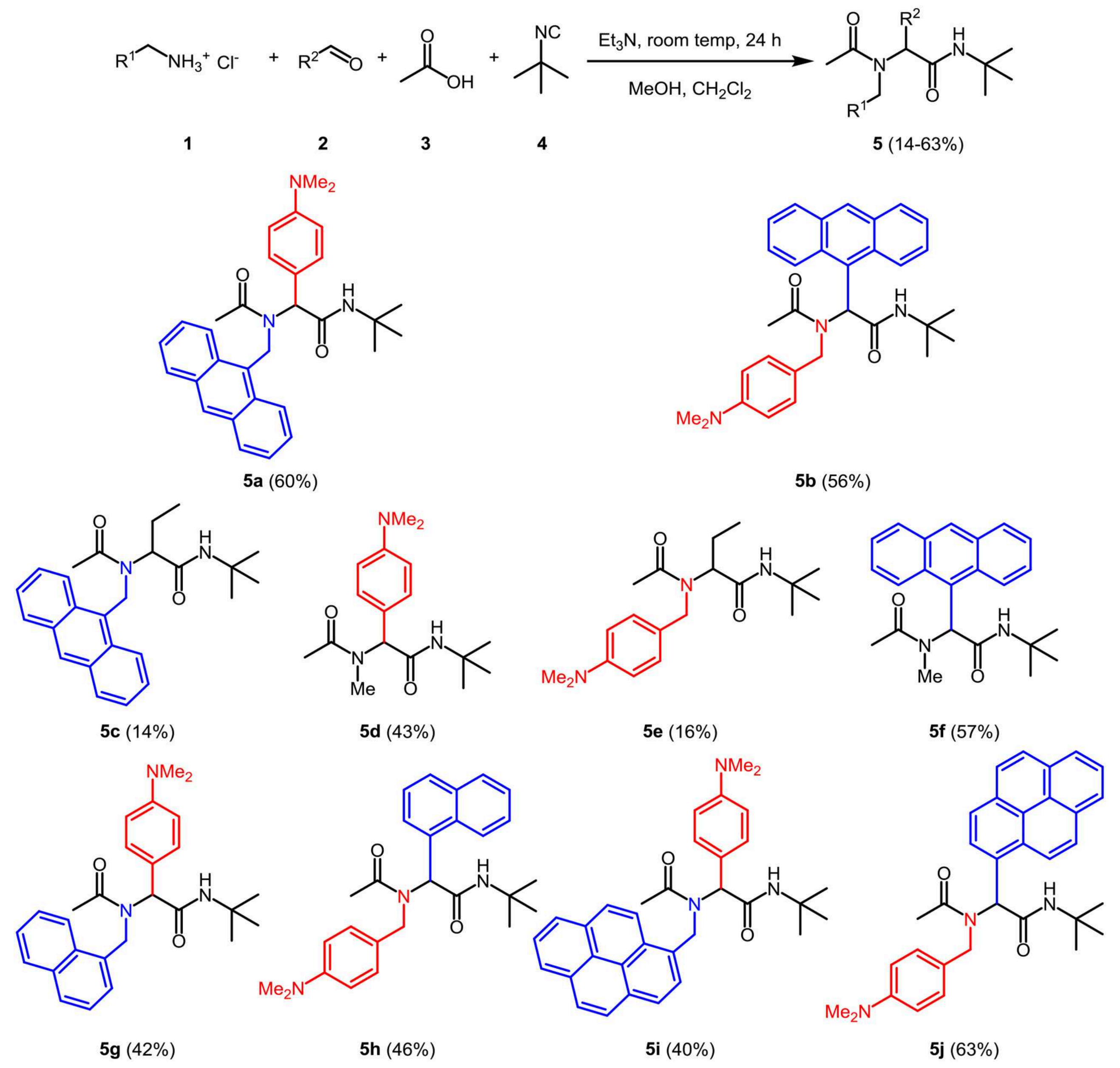
hydrochloride (**1a**) (Stack et al., 2002), commercially available 4-(*N,N*-dimethylamino)benzaldehyde (**2a**), acetic acid (**3**), and *tert*-butylisocyanide (**4**), we set out to identify optimal conditions for the preparation of the targeted potential exciplex system **5** by variation of the base, reaction time, and conditions (see **Table S1**).

The optimal conditions at the equistoichiometric ratio (**Table S1**, entry 6) were therefore employed for the synthesis of other bichromophores and their reference systems **5** in this study, which were obtained in moderate to good yield (**Scheme 1**). For the donor-acceptor bichromophores, 4-*N,N*-dimethylamino phenyl derivatives were used as donor moieties, whereas the acceptor unit was altered from anthracene over pyrene to naphthalene. For solubility issues of pyrene derivatives in methanol, the amount of dichloromethane had to be increased.

The appearance of single-signal sets in the ^{1}H and ^{13}C NMR spectra of **5** unambiguously supports the structural assignment of the bichromophores, and rotamer mixtures due to restricted amide bond rotation can be excluded. The depicted structural assignments were made by identifying the lowest energy conformations by force field calculation scans of the corresponding structures **5**. Distinct resonances in the aromatic region of the spectra account for 9-anthracenyl, 3-pyrenyl, and 1-naphthyl and the *p*-*N,N*-dimethylamino phenyl substitutions, respectively. Mass spectrometry and combustion analysis are additionally in agreement with the structures of bichromophores **5a,b,j-h** and the corresponding reference compounds **5c-f**.

Photophysical Properties

The absorption and emission spectra of all donor-acceptor dyads and their reference compounds were measured in dichloromethane at room temperature (**Table 1**). By comparison of the UV/Vis spectra of *N,N*-dimethylaniline-anthracene dyads **5a** and **5b** with *N,N*-dimethylaniline (**5d** and **5e**) and anthracene (**5c** and **5f**) reference compounds, it can be clearly seen that in the electronic ground state, which is reflected by absorption spectroscopy, no interaction of donor and acceptor subchromophores can be detected by the absence of charge transfer bands. In addition, the spectra of the dyads **5a** and **5b** show an additive behavior with respect to the spectra of the reference compounds **5c** and **5d** and **5e** and **5f**, respectively (**Table 1**). However, in the excited state upon excitation at $\lambda_{exc} = 391$ nm, that is, the longest wavelength absorption band of the anthracene, in the emission spectra besides the anthracene characteristic vibrationally resolved fluorescence for both dyads, **5a** and **5b**, a broad unstructured and redshifted emission band



SCHEME 1 | Ugi 4CR synthesis of donor-acceptor dyads and reference compounds **5**.

at $\lambda_{max,em} = 561$ (dyad **5a**) and 568 nm (dyad **5b**) is detected (**Figure 3**). This redshifted band is most characteristic for the *N,N*-dimethylaniline-anthracene exciplex. With respect to the isomer correlation of the dyads **5a** and **5b** and the essentially identical energy of this transition, it can be concluded that the placement of the aniline and the anthracene can be introduced in either case *via* the aldehyde or the primary amine.

From the comparison of the emission spectra of dyads **5a** and **5b** and the anthracene reference compounds **5c** and **5f** at identical concentration and identical excitation wavelength [$c(\mathbf{5}) = 10^{-5}$ M, $T = 298$ K, $\lambda_{exc} = 391$ nm], it can be clearly seen that for both dyads, a radiative deactivation pathway of the anthracene luminescence by structureless broad exciplex emission bands exists (**Figure 4**). From the relative emission intensities of the exciplex bands and the residual anthracene emission, it can be seen that the exciplex band of dyad **5b** is more intense than that of dyad **5a**. Upon excitation of the dyads **5a** and **5b** at the main absorption bands of the *N,N*-dimethylaniline references **5d** and **5e** ($\lambda_{exc} = 268$ nm), the comparison of the emission spectra reveals that for the dyads, the anthracene emission arises from complete energy transfer from the excited *N,N*-dimethylaniline moieties on expense of the characteristic aniline emission, which can be identified in the emission spectra of the reference compounds **5d** and **5e**

TABLE 1 | Selected absorption and emission spectra of exciplex bichromophores (exciplex emission bands are highlighted in bold face) and reference compounds **5** (recorded in CH_2Cl_2 (chromasolv), $T = 298$ K).

Compound	Absorption λ_{max} [nm] (ε [Lmol^{-1} cm^{-1}])	Emission $\lambda_{max,em}$ [nm]
5a[a]	258 (112,100), 317 (1,600), 335 (2,100), 352 (5,100), 371 (8,300), 391 (7,700)	417, 444, 475, **561**
5b[a]	259 (128,600), 321 (2,300), 339 (3,200), 355 (5,600), 373 (7,800), 393 (6,600)	423, 448, **568**
5c[a]	259 (110,200), 336 (2,800), 352 (6,800), 370 (10,500), 391 (9,800)	418, 443, 471
5d[b]	268 (21,000), 302 (2,500)	353
5e[b]	264 (14,500), 307 (1,100)	356
5f[a]	258 (123,800), 337 (2,500), 353 (5,200), 371 (7,700), 391 (6,900)	420, 445, 475
5g[b]	270 (24,000), 283 (sh), 295 (sh), 309 (sh), 316 (sh), 353 (200)	337, **455**
5h[b]	265 (19,000), 284 (sh), 296 (sh), 312 (sh), 316 (sh), 365 (sh)	334, **472**
5i[c]	258 (sh), 268 (40,600), 278 (48,000), 300 (sh), 317 (13,500), 331 (27,000), 347 (36,000), 377 (800)	383, 397, **499**
5j[c]	259 (sh), 269 (35,600), 279 (43,400), 300 (sh), 317 (14,000), 331 (28,000), 348 (38,000), 377 (900)	380, 395, **538**

[a] *Excitation wavelength $\lambda_{exc} = 391$ nm.* [b] *Excitation wavelength $\lambda_{exc} = 268$ nm.* [c] *Excitation wavelength $\lambda_{exc} = 348$ nm.*

(**Figure 5**). Furthermore, the emission spectrum of dyad **5a** when excited at 268 nm reveals at this excitation wavelength that both the anthracene emission bands and the broad exciplex emission band are can be unambiguously detected (see **Figure S24**). The energy excitation of the exciplex emission arising from reductive electron transfer (from *N,N*-dimethylaniline to excited anthracene) clearly is apparent.

The dyads **5g** and **5h** consist of naphthalene as an acceptor and *N,N*-dimethylaniline as a donor (**Table 2**; **Figure 6**). Upon excitation at $\lambda_{exc} = 268$ nm, the emission spectra reveal weak naphthalene emission bands that are quenched in favor of exciplex emission at 455 and 472 nm, respectively. These differences already indicate that the overlap of naphthalene and *N,N*-dimethylaniline in the sandwich conformer might differ in both isomers.

Likewise and even more pronounced is the difference in exciplex emission of the pyrene-based dyads **5i** and **5j**, which, upon excitation at $\lambda_{exc} = 348$ nm, show well vibrationally resolved pyrene emission bands for isomer **5i** and a broad weaker exciplex band at 499 nm, whereas for isomer **5j** displays a broadened weaker pyrene emission and a more intense, broad exciplex band at 538 nm (**Table 2**; **Figure 7**).

For all three combinations of *N,N*-dimethylaniline-hydrocarbon dyads, exciplex formation occurs by photoexcitation of the hydrocarbon moieties and subsequent interaction with the ground state of the *N,N*-dimethylaniline moiety (Ceroni and Balzani, 2012). The exciplex formation depends on spatial proximity and as a partial electron transfer by the redox potentials of donor and acceptor moieties. The Rehm-Weller approximation (Rehm and Weller, 1970) allows an estimation of the PIET's Gibbs free enthalpy ΔG_{PIET} (Equation 1) by

$$\Delta G_{PIET} = E_0(\mathrm{D}^+/\mathrm{D}) - E_0(\mathrm{A}/\mathrm{A}^-) - E_{00} - \Delta G^0_{solv}[\mathrm{eV}], \quad (1)$$

where $E_0(\mathrm{D}^+/\mathrm{D})$ is the donor's normal oxidation potential, $E_0(\mathrm{A}/\mathrm{A}^-)$ is the acceptor's normal reduction potential (both are often determined from cyclic voltammetry and are given in V), E_{00} is the excitation energy of absorption band in eV (Nishizawa et al., 1998), and ΔG^0_{solv} (in eV) is a correctional term (Equation 2) describing the Coulomb stabilization of two point charges at a distance r_{DA} in a solvent according to

$$\Delta G^0_{solv} = \frac{e^2}{4\pi\varepsilon_0\varepsilon_r r_{DA}} \quad (2)$$

with ε_r (solvent's relative permittivity), ε_0 (vacuum's permittivity, $8.8542 \cdot 10^{-12}$ C V^{-1} m^{-1}), e (elementary charge, $1.6022 \cdot 10^{-19}$ C), and r_{DA} (donor-acceptor distance of the corresponding centroids of the molecule parts).

For *N,N*-dimethylaniline-hydrocarbon dyad conformers with a *syn*-orientation, the Rehm-Weller approximation with literature redox potentials of the constituting donor and acceptor moieties (Kavarnos and Turro, 1986) and MM2-calculated donor-acceptor distances r_{DA} reveals that ΔG_{PIET} is exergonic in all cases (**Table 2**).

The peculiar emission behavior of the dyads **5a, b, g-j** can already be seen upon eyesight under a handheld UV lamp as shown for dyad **5a** in solvents of different polarity and in the solid state (**Figure 8**). A pronounced positive emission solvatochromism, that is, a red shift of the emission with increasing polarity, immediately becomes apparent. The solid state emission band is very broad and unstructured, and the maximum is detected at 474 nm ($\lambda_{exc} = 391$ nm) (see **Figure S32**) and luminesces intensively blue with an external quantum yield $\Phi_f = 0.320$, as determined by an integrating sphere. The broad structureless emission accounts for π-π-stacking of anthracene moieties, as shown for single crystals of 1-acetyl-3-phenyl-5-(9-anthryl)-2-pyrazoline (Feng et al., 2014). As a consequence, the dyad **5a** preferentially adopts the *anti*-conformation in the solid state, where the exciplex emission is absent.

The change of dipole moment from ground to excited state $\mu_E - \mu_G$ can be calculated using the Lippert-Mataga equation (Equation 3),

$$\tilde{\nu}_a - \tilde{\nu}_e = \frac{2\Delta f}{4\pi\varepsilon_0 hca^3}(\mu_E - \mu_G)^2 + const, \quad (3)$$

where $\tilde{\nu}_a$ and $\tilde{\nu}_e$ are the absorption and emission maxima (in cm^{-1}), ε_0 is the vacuum permittivity constant ($8.8542 \cdot 10^{-12}$AsV^{-1}m^{-1}), c is the speed of light (2.9979 ·

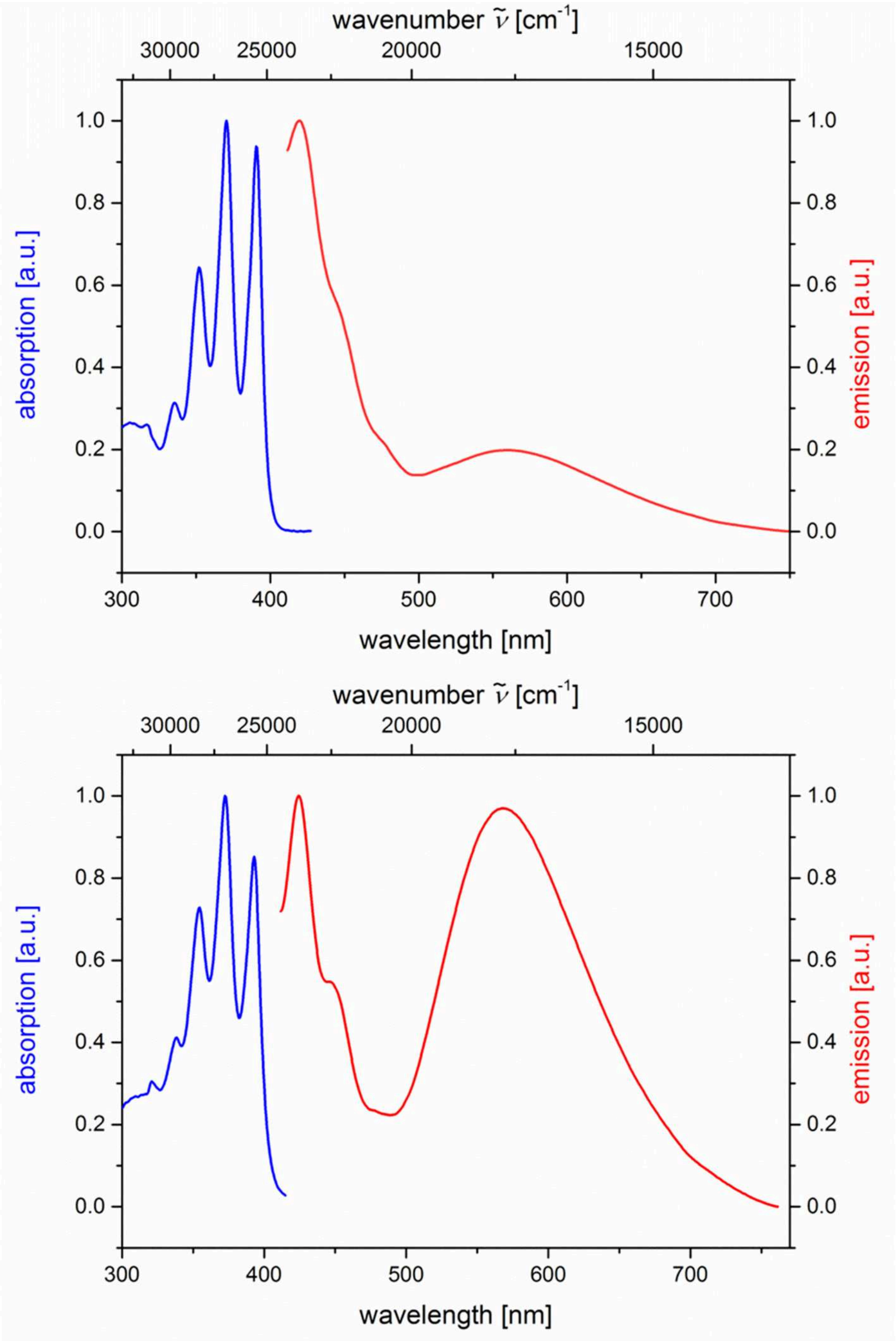


FIGURE 3 | Normalized absorption (blue lines) and emission (red lines) spectra of compounds **5a (top)** and **5b (bottom)** (recorded in CH_2Cl_2 (chromasolv), T = 298 K, λ_{exc} = 391 nm).

10^{10} cms^{-1}), h is the Planck's constant ($6.6256 \cdot 10^{-34}$Js^{-1}), and the orientation polarizability Δf (Equation (4),

$$\Delta f = \frac{\varepsilon_r - 1}{2\varepsilon_r + 1} - \frac{n^2 - 1}{2n^2 + 1} \tag{4}$$

The solvent orientation polarizability Δf of four representative solvents (1,4-dioxane, dichloromethane, acetone, and acetonitrile) gives a very good fit (r^2 = 0.9594) using the Lippert-Mataga plot (Mataga et al., 1956; Lippert, 1957) (see **Figure S42**), the linear correlation of the Stokes shifts $\Delta\tilde{\nu}$ with the relative permittivity ε_r and the optical refractive index n of the

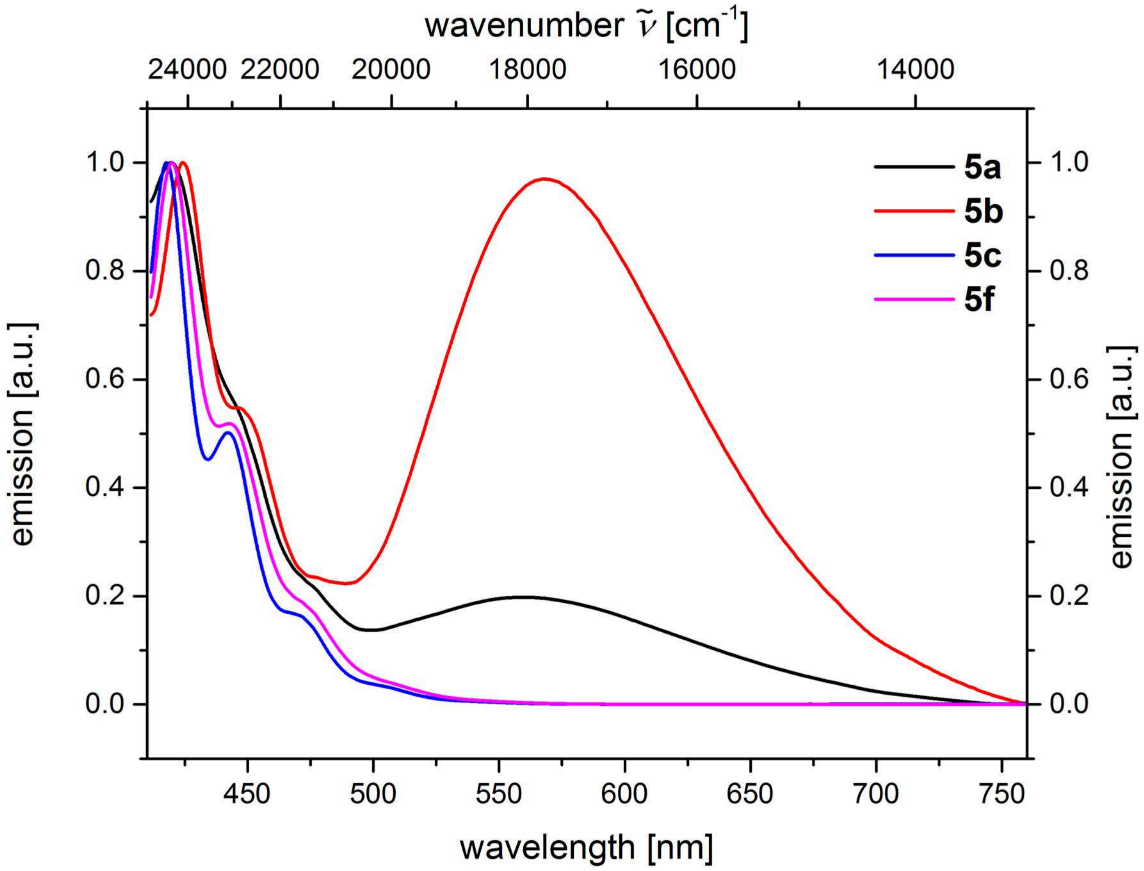


FIGURE 4 | Comparison of emission spectra of compounds **5ac, f** (recorded in CH_2Cl_2 (chromasolv), $c(\mathbf{5}) = 10^{-5}$ M, $T = 298$ K, $\lambda_{exc} = 391$ nm).

corresponding solvent (for details, see **Supplementary Material**). Since *syn*- and *anti*-conformers might be involved in the electronic ground and excited states, we decided to calculate the Onsager radii *a* for both *syn*- and *anti*-conformations from the optimized ground state structures of dyad **5a** by DFT calculations (Frisch et al., 2016) (vide infra). Assuming a *syn*-conformation for dyad **5a** with an Onsager radius of 3.42 Å ($3.42 \cdot 10^{-10}$ m), a change of dipole moment upon excitation from the ground state to the emissive exciplex state $\Delta\mu$ of 6.02 D ($2.008 \cdot 10^{-29}$ Cm) can be calculated. Likewise, for an *anti*-conformation for dyad **5a** with an Onsager radius of 7.92 Å ($7.92 \cdot 10^{-10}$ m), $\Delta\mu$ can be calculated to 21.19 D ($7.067 \cdot 10^{-29}$ Cm).

Calculated Electronic Structure

For further elucidation of the electronic structure, the geometries of three representative dyads **5a**, **5g**, and **5i** in their *syn*- and *anti*-conformations were optimized by DFT calculations using Gaussian 16 (Frisch et al., 2016) with the B3LYP functional (Lee et al., 1988; Becke, 1993; Kim and Jordan, 1994; Stephens et al., 1994) and the Pople 6-311++G** basis set (Krishnan et al., 1980), applying vacuum calculations as well as the Polarizable Continuum Model (PCM) with dichloromethane as a solvent (Scalmani and Frisch, 2010) (for details on the DFT calculations, see **Supplementary Material**). The optimized geometries were verified by frequency analyses of the local minima. Comparison of the calculated ground state energies of the *syn*- and *anti*-conformers reveals that for the anthracene dyad **5a** and for the pyrene dyad **5i**, the *syn*-conformers are stabilized while for the naphthalene dyad **5g**, the *anti*-conformer is slightly favored (**Figure 9**). Equilibrium constants account for a contribution of both conformers in the absorption and, thus, emission behavior of the dyads **5a**, **5g**, and **5i**. The Onsager radii *a* for the *syn*- and *anti*-ground state conformations of dyad **5a** were estimated from the calculated geometry optimization, which led to the Lippert-Mataga plot to the calculation of the change of dipole moment $\Delta\mu$ between the electronic ground state and the vibrationally relaxed exciplex state (vide supra).

Based on the optimized ground state structures of the *anti*- and *syn*-conformers, the electronic absorptions of the three dyads **5a**, **5g**, and **5i** were calculated on the level of TDDFT theory employing the gradient-corrected exchange and correlation Perdew-Burke-Ernzerhof functionals PBE1PBE/6-31G**) (Krishnan et al., 1980; Perdew et al., 1996, 1997; Adamo and Barone, 1999; Ernzerhof and Scuseria, 1999), with dichloromethane (IEFPCM) (Scalmani and Frisch, 2010) as a solvent (for details on the TDDFT calculations, see **Table S4**). The TDDFT calculation of structure *syn*-**5a** gives a lowest energy transition at 431 nm for the S_1 Franck-Condon absorption, which

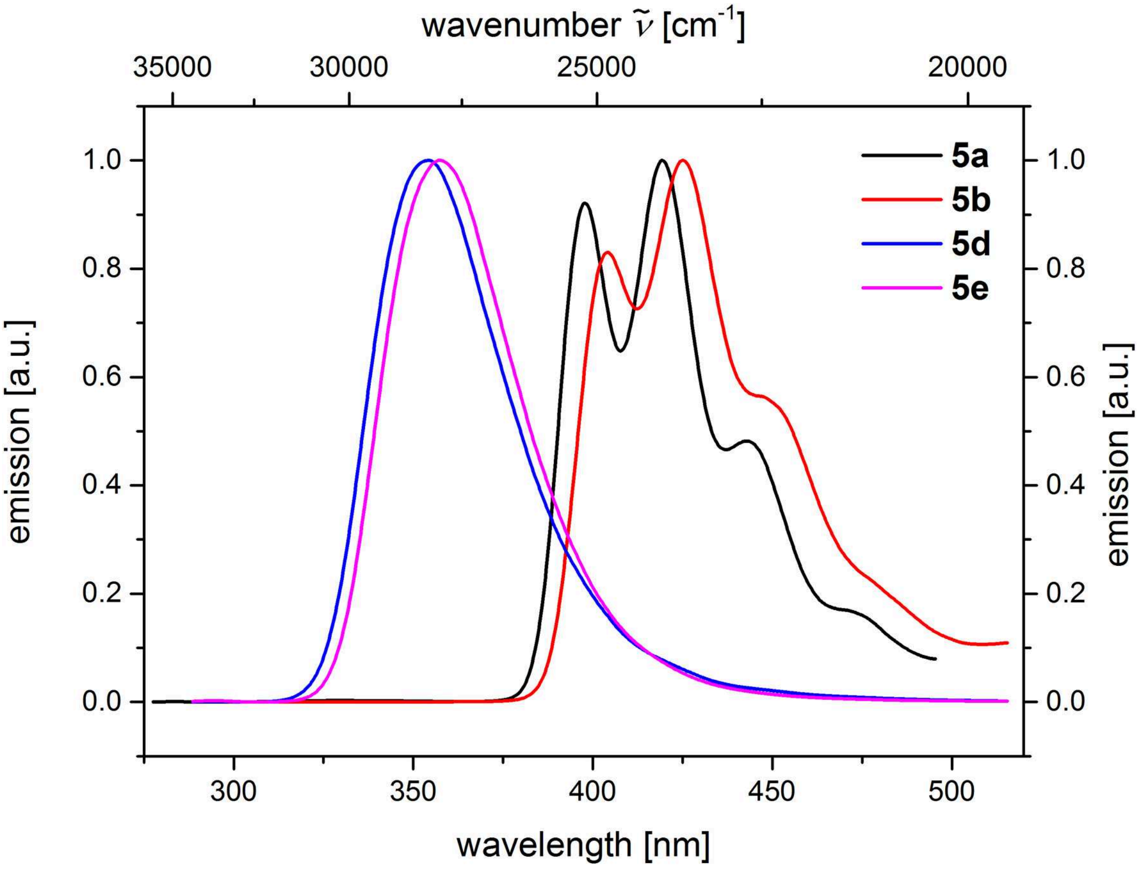


FIGURE 5 | Comparison of emission spectra of compounds **5a** and **5b** (c(**5**) = 10^{-5} M, λ_{exc} = 268 nm), as well as compounds **5d** and **5e** (c(**5**) = 10^{-4} M, λ_{exc} = 258 nm) (recorded in CH_2Cl_2 (chromasolv), T = 298 K).

is represented to 99% as a HOMO to LUMO transition with a significant oscillatory strength of 0.0167 due to coefficient density on both donor and acceptor moieties. This transition represents considerable charge transfer character from the *N,N*-dimethylaniline substituent to the anthracene unit. The experimental spectrum displays an intense structureless band with a maximum at 391 nm, which is in agreement with an excitation of the anthracene part. The calculated S_2 Franck-Condon absorption, which is represented to 98% as a HOMO-1 to LUMO transition with an oscillatory strength of 0.0850, accounts for a dominant anthracene excitation and appears at 388 nm. This transition correlates with the anthracene-type transition at 371 nm in the experimental spectrum. Likewise, the TDDFT calculation of structure *anti*-**5a** gives a lowest energy transition at 415 nm for the S_1 Franck-Condon absorption, which is represented to 99% as a HOMO to LUMO transition with a significant oscillatory strength of 0.003, due to coefficient density on both donor and acceptor moieties. This transition represents considerable charge transfer character from the *N,N*-dimethylaniline substituent to the anthracene unit. The experimental spectrum displays an intense structureless band with a maximum at 391 nm, which is in agreement with an excitation of the anthracene part.

For a general discussion of a model system, the absorption and exciplex emission of dyads *syn*-**5a** and *anti*-**5a** were visualized by plotting in a Jablonski term scheme (**Figure 10**). Starting for structure *syn*-**5a** from the ground state S_0 according to TDDFT calculations Franck-Condon absorption to the vibrationally excited S_2* state proceeds at 380 nm (experiment: 391 nm) as represented by a HOMO-1-LUMO transition, which simultaneously comprises local excitation in the anthracene moiety and coefficient density transfer from *N,N*-dimethylaniline to anthracene (**Figure 10A**). The vibrationally relaxed S_1 state lies 0.751 eV lower in energy. This geometry corresponds to that of the vibrationally excited state S_0*. Therefore, the excitation from the vibrationally excited ground state S_0* to the relaxed first excited state S_1 translates into the process of exciplex fluorescence, which proceeds at 571 nm (experiment: 561 nm). The geometry of the vibrationally excited ground state S_0* lies 0.347 eV above the vibrationally relaxed ground state S_0 and is slightly tighter. This exciplex emission retransmits coefficient density from the anthracene part to the *N,N*-dimethylaniline unit and locally in the anthracene moiety.

Geometrically, the coefficient density in structure *anti*-**5a** is clearly separated in HOMO and LUMO (**Figure 10B**). However, a similar Franck-Condon absorption energy to the vibrationally

TABLE 2 | Rehm-Weller estimation of the PIET's Gibbs free energies ΔG_{PIET} calculated from the energy differences of the redox potentials $E_0(\mathrm{Me_2NPh^+/Me_2NPh}) - E_0(\text{hydrocarbon/hydrocarbon}^-)$, the excitation wavelengths E_{00}, and the solvent correctional term $\Delta G^0{}_{solv}$ for *syn*-conformers of selected dyads **5**.

Compound	$E_0(\mathrm{Me_2NPh}^+/\mathrm{Me_2NPh}) - E_0(\text{hydrocarbon}/\text{hydrocarbon}^-)^a$ [V]	$E_{00}{}^b$ [eV]	$\Delta G^0{}_{solv}{}^c$ [eV]	ΔG_{PIET} [eV]
5a	2.74	3.17[a]	0.44	−0.87
5b	2.74	3.17[a]	0.39	−0.82
5g	3.10	4.63[b]	0.37	−1.90
5h	3.10	4.63[b]	0.33	−1.86
5i	2.85	3.56[c]	0.34	−1.05
5j	2.85	3.56[c]	0.34	−1.05

[a] *Determined from $E_0(\mathrm{Me_2NPh^+/Me_2NPh}) = 0.81$ V, and $E_0(\text{anthracene/anthracene}^-) = -1.93$ V, $E_0(\text{naphthalene/naphthalene}^-) = -2.29$ V, and $E_0(\text{pyrene/pyrene}^-) = -2.04$ V, respectively.* [b] *Calculated from excitation wavelength of **5a** and **5b** ($\lambda_{exc} = 391$ nm), **5g** and **5h** ($\lambda_{exc} = 268$ nm), and **5i** and **5j** ($\lambda_{exc} = 348$ nm).* [c] *Calculated for dichloromethane with a relative permittivity $\varepsilon_r = 8.93$. Donor-acceptor distances r_{DA} taken from MM2 calculations of the conformers with syn-orientation of donor and acceptor (r_{DA}(**5a**) = 3.69 Å; r_{DA}(**5b**) = 4.12 Å; r_{DA}(**5g**) = 4.33 Å; r_{DA}(**5h**) = 4.87 Å; r_{DA}(**5i**) = 4.70 Å; r_{DA}(**5j**) = 4.80 Å).*

excited $S_2{}^*$ state proceeds at 384 nm (experiment: 391 nm), and an almost identical exciplex emission from the vibrationally relaxed S_1 state to the vibrationally excited $S_0{}^*$ state is calculated at 570 nm (experiment: 561 nm). As can be seen from the calculated oscillatory strength (vide supra), the dominant absorption of the *anti*-**5a** conformer is a local excitation of the anthracene moiety, whereas the exciplex emission is completely charge transfer in its character. Expectedly, the oscillatory strength for this process is considerably smaller. Therefore, the experimentally observed exciplex emission preferentially might occur rather from the *syn*-conformer.

Indeed, the simultaneous occurrence of exciplex and hydrocarbon emission in all dyads **5** represents an interesting design principle of novel types of dually emissive bichromophores, arising from selective local excitation followed by acceptor emission as well as redshifted exciplex emission.

CONCLUSION

The Ugi 4CR is an excellent synthetic tool for accessing libraries of donor-acceptor dyads that are covalently ligated, yet, electronically decoupled in the ground state, but electronically coupled in the excited state by virtue of the appearance of exciplex emission. The placement of donor and acceptor moieties has been probed in this study for *N,N*-dimethylaniline as a donor moiety and anthracene, naphthalene, and pyrene as hydrocarbon acceptors with favorable redox potentials for enabling exergonic photo-induced intramolecular electron transfer (PIET) upon local hydrocarbon excitation and estimated by Rehm-Weller approximation. The polar nature of the excited state responsible for exciplex emission is unambiguously assigned by emission solvatochromicity measurement and finally by Lippert-Mataga analysis of the Stokes shifts. The change of dipole moment upon excitation from the ground state to the emissive exciplex state can be calculated to $\Delta\mu = 6.02$ D for the *syn*-conformer of the *N,N*-dimethylaniline-anthracene dyad and to $\Delta\mu = 21.19$ D for the corresponding *anti*-conformer. For the same dyad, TDDFT calculations with the gradient-corrected exchange and correlation Perdew-Burke-Ernzerhof functionals PBE1PBE were carried out, allowing a qualitative assignment of the experimental absorption and emission bands and, thus, rationalizing the particular relevance of the exciplex' electronic structure. In conclusion, the synthetic scaffold concept employing the isonitrile-based Ugi 4CR enables the design and photophysical proof of concept of novel types of unimolecular exciplex emitters. In principle, even unimolecular multichromophore arrays can be quickly assembled according to the same principle. Synthetic and photophysical studies of dually emissive unimolecular multichromophores are currently underway.

EXPERIMENTAL

General Considerations

All reactions were performed in oven-dried Schlenk vessels under a nitrogen atmosphere. The employed solvents were dried with a solvent drying system *MB-SPS 800* by *M. Braun Inertgas-Systeme GmbH* and used as obtained. Commercial grade reagents were used as supplied without further purification and were purchased from abcr GmbH & Co. KG, Acros Organics, Alfa Aesar GmbH & Co. KG, Sigma-Aldrich Chemie GmbH. The purification of Ugi-compounds **5** was performed by column chromatography on silica gel 60 M (0.04–0.063 mm) from Macherey-Nagel GmbH & Co. KG using flash technique under pressure of 2 bar. The crude mixtures were adsorbed on Celite® 545 from Carl Roth GmbH Co. KG before chromatographic purification. The reaction progress was monitored qualitatively using TLC Silica gel 60 F254 aluminum sheets obtained from Merck KGaA, Darmstadt. The spots were detected with UV light at 254 nm and using an iodine chamber. ^{1}H, ^{13}C, and 135-DEPT ^{13}C NMR spectra were recorded on Bruker Avance DRX 300 and Bruker Avance DRX 500. $CDCl_3$ and DMSO-d_6 were used as deuterated solvents. The resonances of the solvents were locked as internal standards ($CDCl_3$: ^{1}H δ 7.27, ^{13}C δ 77.23; DMSO-d_6: ^{1}H δ 2.50, ^{13}C δ 39.5). The muliplicities of the signals were abbreviated as follows: s: singlet; d: doublet; dd: doublet of doublets; t: triplet; m: multiplet. The type of carbon nucleus was determined on the basis of 135-DEPT ^{13}C NMR spectra. For the description of the ^{13}C NMR spectra primary carbon nuclei are abbreviated with CH_3, secondary carbon nuclei with CH_2, tertiary carbon nuclei with CH, and quaternary carbon nuclei with $C_{quat.}$. MALDI mass spectra were measured on a Bruker Ultraflex spectrometer, ESI mass spectra were measured on an Ion-Trap-API-mass spectrometer of Finnigan LCQ Deca (Thermo Quest). IR spectra were obtained on a Shimadzu IRAffinity-1, which works with the attenuated total reflection (ATR) method. The intensity

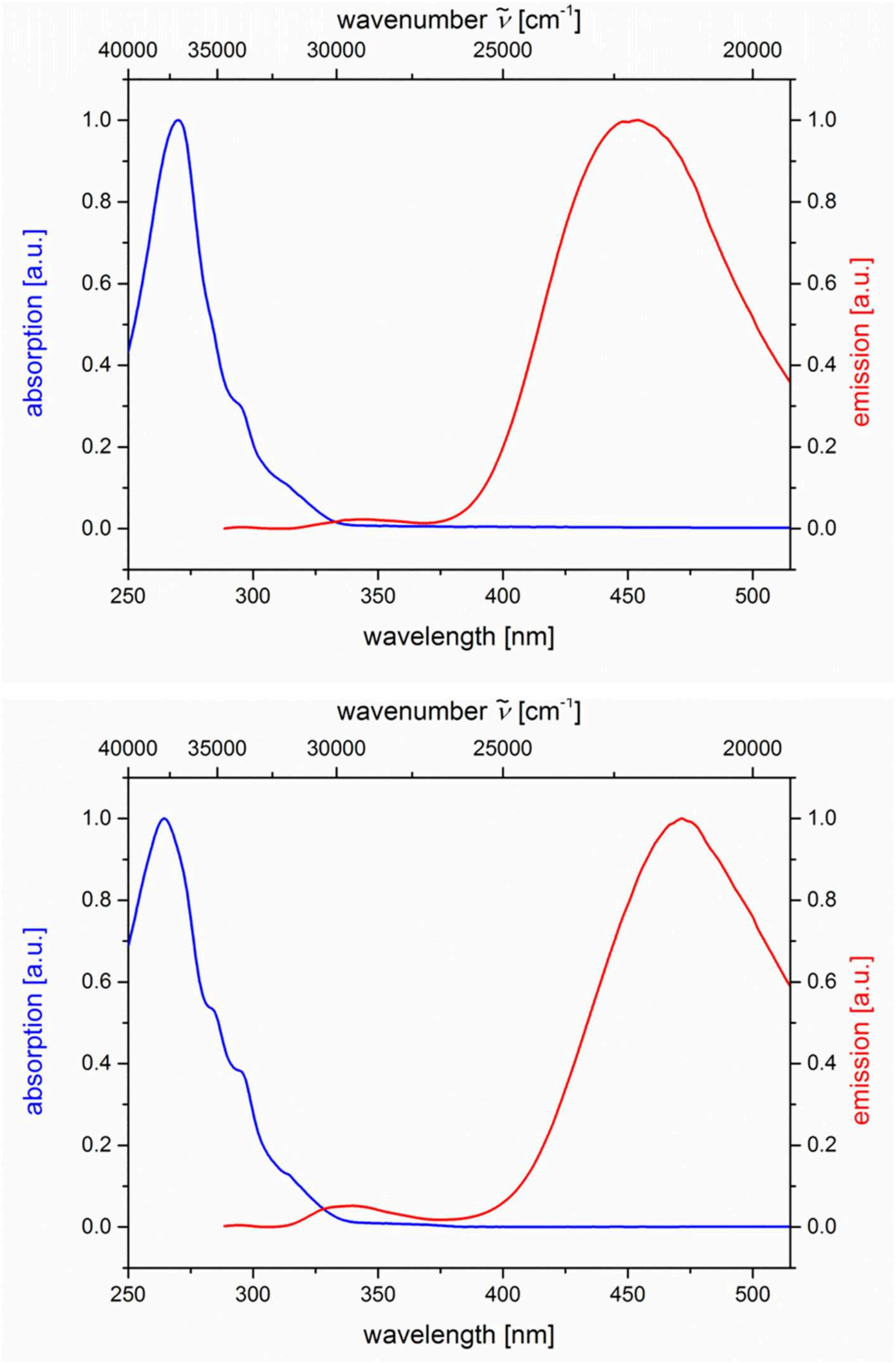


FIGURE 6 | Normalized absorption (blue lines) and emission (red lines) spectra of compounds **5g (top)** and **5h (bottom)** (recorded in CH_2Cl_2 (chromasolv), T = 298 K, λ_{exc} = 268 nm).

of signals is abbreviated as follows: s (strong), m (medium), w (weak). UV/Vis spectra were recorded on a Lambda 19 spectrometer (Perkin Elmer) in dichloromethane at $T = 293$ K. Emission spectra were recorded on a Hitachi F-7000 instrument in dichloromethane and concentrations of 10^{-6} mol L^{-1} at $T = 293$ K. Data analysis was done with the software FL solutions 4.0 by Hitachi. The melting points (uncorrected) were measured on a Büchi Melting Point B-540 apparatus. Combustion analyses were carried out on a vario Micro Cube by Elementaranalysentechnik in the Microanalytical Laboratory of the Institut für Pharmazeutische und Medizinische Chemie der Heinrich-Heine-Universität Düsseldorf.

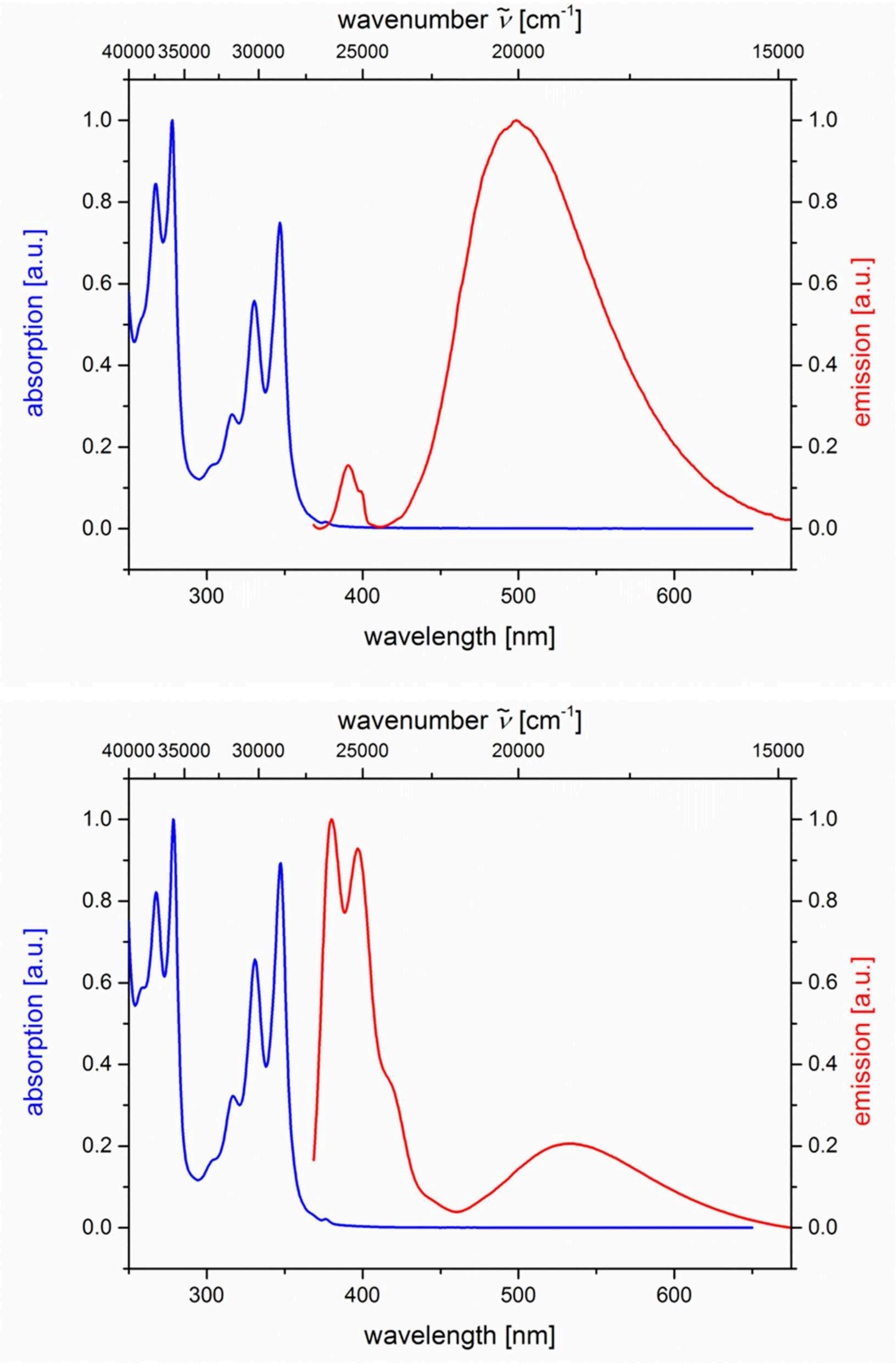


FIGURE 7 | Normalized absorption (blue lines) and emission (red lines) spectra of compounds **5i (top)** and **5j (bottom)** (recorded in CH_2Cl_2 (chromasolv), $T = 298\,K$, $\lambda_{exc} = 348\,nm$).

General Procedure (GP) for the Ugi-4CR Synthesis of Exciplex Bichromophores and Reference Compounds 5

In a 25-mL Schlenk tube with a magnetic stir bar were placed methylamine hydrochloride **1** (0.50 mmol), triethylamine (0.07 mL, 0.50 mmol), and methanol, and the mixture was stirred for 30 min (for experimental details, see **Table 3**). Then, aldehyde **2** (0.50 mmol) dissolved in dichloromethane was added dropwise, and the reaction mixture was stirred for 1 h. Finally, acetic acid (**3**) (0.50 mmol) and *tert*-butyl isocyanide (**4**) (0.06 mL, 0.50 mmol) were added, and reaction mixture was stirred at room temperature for 24 h. After removal of the solvents, the crude products were purified by flash chromatography on silica gel (*n*-hexane/ethyl acetate) and crystallized from various solvents or solvent mixtures to give analytically pure Ugi-4CR products as colorless to yellow solids.

FIGURE 8 | Dyad **5a** in the solid state and in cyclohexane, toluene, 1,4-dioxane, and dichloromethane solutions (from left to right) under a handheld UV lamp (λ_{exc} = 365 nm).

2-(*N*-(9-Anthrylmethyl)acetamido)-*N*-(tert-butyl)-2-(4-(dimethylamino)phenyl) acetamide (5a)

According to the GP and after chromatography on silica gel (*n*-hexane/ethyl acetate 3:2) and crystallization from hexane/ethanol (50:3), compound **5a** (144 mg, 60%) was obtained as a light yellow solid, Mp 186–187°C, R$_f$ (*n*-hexane/ethyl acetate 1:1) = 0.40.

^{1}H NMR (300 MHz, CDCl$_3$): δ = 0.83 (s, 9 H), 1.98 (s, 3 H), 2.90 (s, 6 H), 4.69 (d, *J* = 14.7 Hz, 1 H), 4.69 (s, 1 H), 5.38 (d, *J* = 14.7 Hz, 1 H), 6.26 (d, *J* = 14.1 Hz, 1 H), 6.51–6.69 (m, 2 H), 6.74–6.92 (m, 2 H), 7.387.63 (m, 4 H), 8.03 (d, *J* = 7.5 Hz, 2 H), 8.22 (d, *J* = 7.2 Hz, 2 H), 8.48 (s, 1 H). ^{13}C NMR (75 MHz, CDCl$_3$): δ = 24.1 (CH$_3$), 28.3 (CH$_3$), 40.6 (CH$_3$), 41.8 (CH$_2$), 51.3 (C$_{quat}$), 62.9 (CH), 112.4 (CH), 122.0 (C$_{quat}$), 124.0 (CH), 125.5 (CH), 127.5 (CH), 128.0 (C$_{quat}$), 128.6 (CH), 129.0 (CH), 129.6 (CH), 131.6 (C$_{quat}$), 131.7 (C$_{quat}$), 150.0 (C$_{quat}$), 168.3 (C$_{quat}$), 173.5 (C$_{quat}$). MALDI-TOF-MS (*m/z*): 480.1 ([M]$^+$). IR: $\tilde{\nu}$ [cm^{-1}] = 3,298 (w); 3,055 (w); 2,957 (w); 2,910 (w); 2,863 (w); 2,806 (w); 1,678 (s); 1,614 (s); 1,549 (m); 1,526 (s); 1,481 (w); 1,445 (m); 1,418 (w); 1,391 (w); 1,358 (m); 1,339 (w); 1,325 (w); 1,306 (w); 1,285 (w); 1,256 (w); 1,227 (m); 1,209 (w); 1,193 (w); 1,188 (w); 1,167 (w); 1,167 (w); 1,140 (w); 1,063 (w); 1,040 (w); 1,024 (w); 988 (w); 949 (w); 881 (m); 841 (w); 827 (w); 812 (w); 791 (s); 735 (s); 694 (w); 660 (w); 642 (w); 625 (w). UV/Vis (CH$_2$Cl$_2$): λ_{max} (ε [Lmol^{-1} cm^{-1}]) [nm] = 352 (5,100), 417 (8,300), 391 (7,700). Fluorescence (CH$_2$Cl$_2$): $\lambda_{max,em}$ [nm] = 417, 444, 475, 561; Stokes shift $\Delta\tilde{\nu}$ = 1,600 cm^{-1}. Anal. calcd. for C$_{31}$H$_{35}$N$_3$O$_2$ (481.3): C 77.31, H 7.32, N 8.72; Found: C 77.03, H 7.31, N 8.57.

2-(9-Anthryl)-*N*-(tert-butyl)-2-(*N*-(4-(dimethylamino)phenyl) acetamide) (5b)

According to the GP and after chromatography on silica gel (*n*-hexane/ethyl acetate 3:2) and crystallization from hexane/ethyl acetate (55:5), compound **5b** (134 mg, 56%) was obtained as a yellow solid, Mp 192°C, R$_f$ (*n*-hexane/ethyl acetate 1:1) = 0.50.

^{1}H NMR (300 MHz, CDCl$_3$): δ = 1.211.23 (m, 0.5 H), 1.23 (s, 9 H), 2.02 (s, 0.5 H), 2.16 (s, 3 H), 2.63 (s, 6 H), 4.10 (q, *J* = 7.2 Hz, 0.3 H) 4.464.71 (m, 2 H), 5.06 (s, 1 H), 6.02 (d, *J* = 8.7 Hz, 2 H), 6.14 (d, *J* = 8.6 Hz, 2 H), 7.407.59 (m, 4 H), 7.63 (s, 1 H), 7.92 (d, *J* = 7.6 Hz, 2 H), 8.36 (s, 1 H), 8.37 (d, *J* = 8.5 Hz, 2 H). ^{13}C NMR (75 MHz, CDCl$_3$): δ = 14.35 (CH$_3$), 21.18 (CH$_3$), 22.94 (CH$_3$), 28.71 (CH$_3$), 40.74 (CH$_3$), 50.14 (CH$_2$), 51.94 (C$_{quat}$), 57.62 (CH), 60.53 (CH$_2$), 112.27 (CH), 124.96 (CH), 125.14 (CH), 125.73 (C$_{quat}$), 126.25 (C$_{quat}$), 126.56 (CH), 127.28 (CH), 129.58 (CH), 130.57 (CH), 131.63 (C$_{quat}$), 132.29 (C$_{quat}$), 149.24 (C$_{quat}$), 171.05 (C$_{quat}$), 171.28 (C$_{quat}$), 173.01 (C$_{quat}$). MALDI-TOF-MS (*m/z*): 480.1 ([M]$^+$), 450.9 ([M – 2 CH$_3$]$^+$), 269.9 ([M – C$_{11}$H$_{16}$N$_2$O]$^+$). IR: $\tilde{\nu}$ [cm^{-1}] = 3,422 (w) 2,979 (w); 2,882 (w); 2,849 (w); 2,799 (w); 1,736 (s); 1,680 (s); 1,620 (s); 1,514 (s); 1,449 (m); 1,406 (m); 1,391 (m); 1,364 (m); 1,256 (m); 1,341 (m); 1,327 (w); 1,314 (w); 1,287 (w); 1,275 (w); 1,258 (w); 1,223 (m); 1,192 (m); 1,169 (w); 1,070 (w); 1,036 (w); 1,022 (w); 997 (w); 968 (w); 949 (w); 939 (w); 908 (w); 853 (w); 812 (w); 785 (m); 741 (s). UV/Vis (CH$_2$Cl$_2$): λ_{max} (ε [Lmol^{-1} cm^{-1}]) [nm] = 355 (5,600), 373 (7,800), 393 (6,600). Fluorescence (CH$_2$Cl$_2$): $\lambda_{max,em}$ [nm] = 423, 448, 568. Stokes shift $\Delta\tilde{\nu}$ = 1,800 cm^{-1}. Anal. calcd. for C$_{31}$H$_{35}$N$_3$O$_2$ 1/6 CH$_3$CO$_2$C$_2$H$_5$ (481.3 + 14.7): C 76.59, H 7.35, N 8.51; Found: C 76.24, H 7.21, N 8.54.

2-(*N*-(9-Anthrylmethyl)acetamido)-*N*-tert-butylbutanamide (5c)

According to the GP and after chromatography on silica gel (*n*-hexane/ethyl acetate 2:1) and crystallization from hexane/ethyl acetate (6.5:0.5), compound **5c** (32.1 mg, 14%) was obtained as a yellow crystalline solid, Mp 150°C, R$_f$ (*n*-hexane/ethyl acetate 2:1) = 0.20.

^{1}H NMR (300 MHz, CDCl$_3$): δ = 0.52 (s, 9 H), 1.09 (t, *J* = 7.5 Hz, 3 H), 1.35 (m, 1H), 2.04 (s, 3 H), 2.132.34 (m, 1H), 3.48 (t, *J* = 7.2 Hz, 1 H), 4.38 (s, 1 H), 4.91 (d, *J* = 15.0 Hz, 1 H), 6.59 (d, *J* = 15.0 Hz, 1 H), 7.407.65 (m, 4 H), 8.03 (d, *J* = 8.4 Hz, 2 H), 8.33 (d, *J* = 8.8 Hz, 2 H), 8.48 (s, 1 H). ^{13}C NMR (75 MHz, CDCl$_3$): δ = 12.3 (CH$_3$), 22.8 (CH$_3$), 24.1 (CH$_2$), 27.8 (CH$_3$), 42.0 (CH$_2$), 50.6 (C$_{quat}$), 61.3 (CH), 123.6 (CH), 125.7 (CH), 127.6 (C$_{quat}$), 128.0 (CH), 129.2 (CH), 130.0 (CH), 131.5 (C$_{quat}$), 131.7 (C$_{quat}$), 169.4 (C$_{quat}$), 171.8 (C$_{quat}$). MALDI-TOF-MS (*m/z*): 391.0 ([M]$^+$), 347.0 ([M – OC$_2$H$_3$]$^+$). UV/Vis (CH$_2$Cl$_2$): λ_{max} (ε [Lmol^{-1} cm^{-1}]) [nm] = 352 (6,800), 370 (10,500), 391 (9,800). Fluorescence (CH$_2$Cl$_2$): $\lambda_{max,em}$ [nm] = 418, 443, 471. Stokes shift $\Delta\tilde{\nu}$ = 1,700 cm^{-1}. Anal. calcd. for

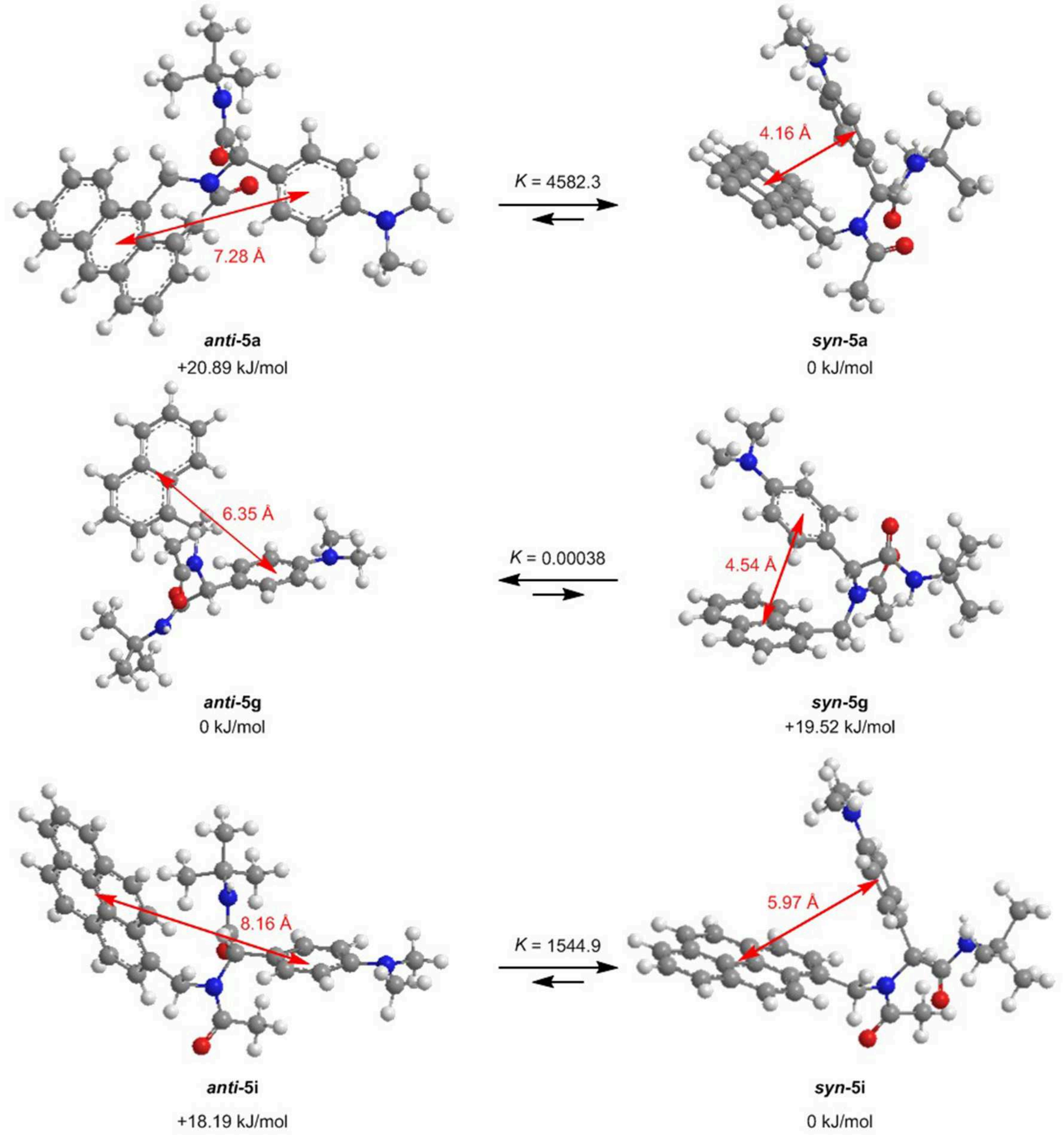


FIGURE 9 | Ground state *anti-syn*-conformation equilibria (Δ*G*, *K*) and donor-acceptor centroid distances according to DFT calculations on the minimum energy conformers of dyads **5a**, **5g**, and **5i** (B3LYP/6-311++G** at *T* = 298 K).

$C_{25}H_{30}N_2O_2$ (390.2): C 76.89, H 7.74, N 7.17; Found: C 76.88, H 7.78, N 6.99.

N-tert-butyl-2-(4-(dimethylamino)phenyl)-2-(*N*-methylacetamido)acetamide (5d)

According to the GP and after chromatography on silica gel (*n*-hexane/ethyl acetate 1:1) and crystallization from hexane/ethyl acetate (25:2.5), compound **5d** (92.4 mg, 43%) was obtained as a light brown solid, Mp 155°C, R_f (*n*-hexane/ethyl acetate 1:1) = 0.10.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.30 (s, 9 H), 2.09 (s, 3 H), 2.80 (s, 3 H), 2.93 (s, 6 H), 5.52 (s, 1H), 6.07 (s, 1 H), 6.66 (d, J = 8.7 Hz, 2 H), 7.15 (d, J = 8.7 Hz, 2 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 22.36 (CH_3), 28.84 (CH_3), 33.16 (CH_3), 40.52 (CH_3), 51.67 (C_{quat}), 60.13 (CH), 112.43 (CH), 122.96 (C_{quat}), 130.44 (CH), 150.36 (C_{quat}), 169.84 (C_{quat}), 171.56 (C_{quat}). MALDI-TOF-MS (m/z): 304.3 ($[M]^+$). IR: $\tilde{\nu}$ [cm^{-1}] = 3,287 (w); 2.965 (w); 2.918 (w); 2,895 (w); 2,806 (w); 1,680 (s); 1,612 (s); 1,551 (m); 1,522 (s); 1,503 (w); 1,474 (w); 1,443 (w); 1,431 (w); 1,404 (m); 1,387 (w); 1,375 (w); 1,350 (m); 1,281 (w); 1,254 (w); 1,227 (m); 1,204 (w); 1,182 (w); 1,169 (w); 1,144 (w); 1,126 (w); 1,065 (w); 1,022 (m); 959 (w); 945 (m); 829 (w); 812 (w); 797 (m); 745 (w); 694 (w); 640 (w). UV/Vis (CH_2Cl_2): λ_{max} (ε [$Lmol^{-1}$ cm^{-1}]) [nm] = 268 (21,000). Fluorescence (CH_2Cl_2): $\lambda_{max,em}$

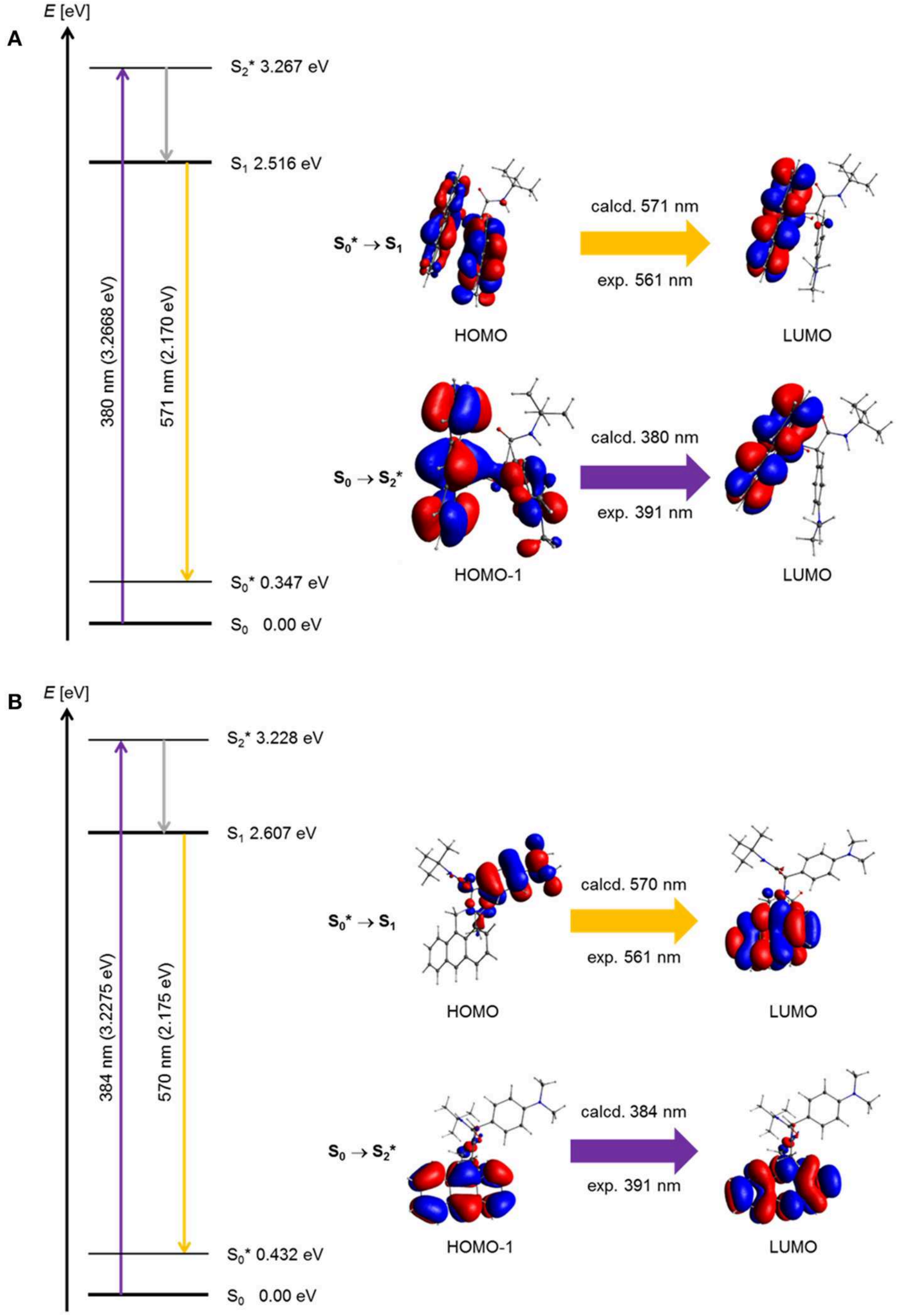


FIGURE 10 | Jablonski diagrams of dyads **(A)** *syn*-**5a** and **(B)** *syn*-**5b** with assignment of the FMO-transitions in the experimental and calculated longest wavelength absorption bands and the exciplex emission bands [$E(S_0) = 0$ eV; PBE1PBE 6-31G** IEFPCM CH_2Cl_2, isosurface value at 0.03 a.u.].

[nm] = 353. Stokes shift $\Delta\tilde{\nu} = 9{,}000$ cm^{-1}. Anal. calcd. for $C_{17}H_{27}N_3O_2$ (305.2): C 66.85, H 8.91, N 13.76; Found: C 66.58, H 8.86, N 13.46.

N-tert-butyl-2-(*N*-(4-(dimethylamino)benzyl) acetamido)butanamide (5e)

According to the GP and after chromatography on silica gel (*n*-hexane/ethyl acetate 2:1) and crystallization from hexane/ethyl acetate (5:0.5), compound **5e** (31.5 mg, 16%) was obtained as a dark yellow solid, Mp 106°C, R$_f$ (*n*-hexane/ethyl acetate 1:1) = 0.30.

^{1}H NMR (300 MHz, CDCl$_3$): $\delta = 0.80$ (t, $J = 7.3$ Hz, 3 H), 1.25 (s, 9 H), 1.731.98 (m, 2 H), 2.06 (s, 3 H), 2.88 (s, 6 H), 4.48 (s, 2 H), 4.584.67 (m, 1 H), 6.34 (s, 1 H), 6.64 (d, $J = 8.7$ Hz, 2 H), 7.00 (d, $J = 8.6$ Hz, 2 H). ^{13}C NMR (75 MHz, CDCl$_3$): $\delta = 11.1$ (CH$_3$), 21.9 (CH$_2$), 22.6 (CH$_3$), 28.8 (CH$_3$), 40.6 (CH$_3$), 48.9 (CH$_2$), 51.2

TABLE 3 | Experimental details of the Ugi-4CR synthesis of exciplex bichromophores and reference compounds 5.

Entry	MeOH [mL]	CH_2Cl_2 [mL]	$R^1CH_2NH_3^+Cl^-$ 1 [mg] (mmol)	R^2CHO 2 [mg] (mmol)	Acetic acid (3) [mg] (mmol)	Yield [mg] (%)[a]
1	1.00	0.25	123 (0.50) of **1a**	79.8 (0.52) of **2a**	30.0 (0.50)	144 (60) of **5a**
2[b]	1.00	0.25	121 (0.54) of **1b**	105.6 (0.51) of **2b**	30.0 (0.50)	134 (56) of **5b**
3	1.00	0.25	146 (0.60) of **1a**	34.8 (0.60) of **2c**	36.0 (0.60)	32.1 (14) of **5c**
4	1.00	0.25	47.9 (0.70) of **1c**	110 (0.72) of **2a**	42.0 (0.70)	92.4 (43) of **5d**
5[b]	1.00	0.25	137 (0.61) of **1b**	34.8 (0.60) of **2c**	36.0 (0.60)	31.5 (16) of **5e**
6	1.25	0.50	48.0 (0.71) of **1c**	144.4 (0.70) of **2b**	42.0 (0.70)	145 (57) of **5f**
7[c]	1.00	0.25	78.6 (0.50) of **1d**	79.1 (0.53) of **2a**	30.0 (0.50)	91.7 (42) of **5g**
8[b]	1.00	0.25	118 (0.52) of **1b**	78.1 (0.50) of **2d**	30.0 (0.50)	99.1 (46) of **5h**
9	0.75	0.50	142 (0.50) of **1e**	78.1 (0.51) of **2a**	30.0 (0.50)	102 (40) of **5i**
10[b]	1.00	1.00	119 (0.53) of **1b**	117 (0.51) of **2e**	30.0 (0.50)	160 (63) of **5j**

*[a] Isolated yield after flash chromatography. [b] Methyl ammonium chloride **1b** was employed as a bishydrochloride and, therefore, the amount of triethylamine was doubled (0.14 mL, 1.00 mmol). [c] No triethylamine was added (**1d** was employed as the free base).*

(C_{quat}), 60.5 (CH), 112.9 (CH), 125.3 (C_{quat}), 127.2 (CH), 150.0 (C_{quat}), 170.1 (C_{quat}), 173.1 (C_{quat}). MALDI-TOF-MS (*m/z*): 332.0 ($[M]^+$). UV/Vis (CH_2Cl_2): λ_{max} (ε [$Lmol^{-1}$ cm^{-1}]) [nm] = 264 (14,500), 321 (1,300). Fluorescence (CH_2Cl_2): $\lambda_{max,\,em}$ [nm] = 356. Stokes shift $\Delta\tilde{\nu}$ = 9,800 cm^{-1}. Anal. calcd. for $C_{19}H_{31}N_3O_2$ (333.2): C 68.43, H 9.37, N 12.60; Found: C 68.18, H 9.36, N 12.35.

2-(9-Anthryl)-*N*-(tert-butyl)-2-(*N*-methylacetamido) acetamide (5f)

According to the GP and after chromatography on silica gel (*n*-hexane/ethyl acetate 2:1) and crystallization from hexane/ethyl acetate (30:3), compound **5f** (145 mg, 57%) was obtained as a colorless solid, Mp 260–262°C, R_f (*n*-hexane/ethyl acetate 2:1) = 0.10.

^1H NMR (300 MHz, $CDCl_3$): δ = 1.21 (s, 9 H), 2.22 (s, 3 H), 2.85 (s, 3 H), 4.95 (s, 1 H), 7.397.58 (m, 4 H), 7.49 (s, 1 H), 7.988.05 (m, 2 H), 8.28 (d, *J* = 9.0 Hz, 2 H), 8.52 (s, 1 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 22.4 (CH_3), 28.7 (CH_3), 33.3 (CH_3), 51.86 (C_{quat}), 56.6 (CH), 125.0 (CH), 125.3 (CH), 126.2 (C_{quat}), 127.3 (CH), 129.6 (CH), 130.4 (CH), 131.7 (C_{quat}), 132.2 (C_{quat}), 170.6 (C_{quat}), 171.3 (C_{quat}). MALDI-TOF-MS (*m/z*): 363.2 ($[M]^+$), 290.2 ($[M - NHC(CH_3)_3]^+$). IR: $\tilde{\nu}$ [cm^{-1}] = 3,327 (w); 3.046 (w); 2,967 (w); 2,930 (w); 2,899 (w); 2,870 (w); 1,684 (s); 1,632 (s); 1,533 (m); 1,472 (w); 1,452 (m); 1,375 (w); 1,358 (m); 1,335 (w); 1,323 (m); 1,281 (w); 1,256 (w); 1,227 (w); 1,188 (w); 1,163 (w); 1,130 (w); 1,107 (w); 1,055 (w); 1,020 (w); 1,001 (w); 991 (w); 961 (w); 941 (w); 926 (w); 897 (m); 874 (w); 851 (m); 820 (w); 787 (w); 733 (s); 638 (w). UV/Vis (CH_2Cl_2): λ_{max} (ε [$Lmol^{-1}$ cm^{-1}]) [nm] = 353 (5,200), 371 (7,700), 391 (6,900). Fluorescence (CH_2Cl_2): $\lambda_{max,em}$ [nm] = 420, 445, 475. Stokes shift $\Delta\tilde{\nu}$ = 1,800 cm^{-1}. Anal. calcd. for $C_{23}H_{26}N_2O_2$ (362.2): C 76.21, H 7.23, N 7.73; Found: C 75.93, H 7.18, N 7.72.

N-(tert-butyl)-2-(4-(dimethylamino)phenyl)-2-(*N*-(1-naphthylmethyl)acetamide) acetamide (5g)

According to the GP and after chromatography on silica gel (*n*-hexane/ethyl acetate 1:1) and crystallization from hexane/ethyl acetate (30:2) compound **5g** (91.7 mg, 42%) was obtained as a colorless solid, Mp 174°C, R_f (*n*-hexane/ethyl acetate 1:1) = 0.50.

^1H NMR (300 MHz, $CDCl_3$): δ = 1.34 (s, 9 H), 2.01 (s, 3 H), 2.77 (s, 6 H), 4.875.32 (m, 2 H), 5.53 (s, 1 H), 5.90 (s, 1 H), 6.42 (d, *J* = 8.5 Hz, 2 H), 7.19 (d, *J* = 8.5 Hz, 2 H), 7.267.34 (m, 2 H), 7.377.50 (m, 2 H), 7.557.67 (m, 1 H), 7.737.86 (m, 2 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 22.3 (CH_3), 28.8 (CH_3), 40.4 (CH_3), 47.9 (CH_2), 51.7 (C_{quat}), 62.9 (CH), 112.3 (CH), 122.1 (C_{quat}), 122.3 (CH), 123.4 (CH), 125.5 (CH), 125.7 (CH), 126.1 (CH), 127.2 (CH), 128.9 (CH), 130.3 (C_{quat}), 130.9 (CH), 133.0 (C_{quat}), 133.5 (C_{quat}), 150.4 (C_{quat}), 169.9 (C_{quat}), 172.9 (C_{quat}). MALDI-TOF-MS (*m/z*): 430.1 ($[M]^+$). IR: $\tilde{\nu}$ [cm^{-1}] = 3,314 (w); 3,049 (w); 2,968 (w); 2,912 (w); 2,886 (w); 2,808 (w); 1,676 (m); 1,632 (s); 1,616 (m); 1,601 (w); 1,541 (m); 1,522 (m); 1,507 (w); 1,477 (w); 1,447 (w); 1,423 (m); 1,391 (w); 1,358 (m); 1,319 (w); 1,261 (w); 1,250 (w); 1,227 (m); 1,206 (w); 1,190 (m); 1,165 (w); 1,126 (w); 1,063 (w); 1,047 (w); 1,032 (w); 978 (w); 939 (w); 827 (w); 802 (m); 789 (s); 772 (s); 750 (w); 735 (w); 687 (w); 640 (w); 625 (w). UV/Vis (CH_2Cl_2): λ_{max} (ε [$Lmol^{-1}$ cm^{-1}]) [nm] = 270 (24,000). Fluorescence (CH_2Cl_2): $\lambda_{max,em}$ [nm] = 337, 455. Stokes shift $\Delta\tilde{\nu}$ = 7,400 cm^{-1}. Anal. calcd. for $C_{27}H_{33}N_3O_2$ (431.3): C 75.14, H 7.71, N 9.74; Found: C 75.15, H 7.58, N 9.67.

N-tert-butyl-2-(*N*-(4-(dimethylamino)benzyl) acetamido)-2-(1-naphthyl)acetamide (5h)

According to the GP and after chromatography on silica gel (*n*-hexane/ethyl acetate 1:1) and crystallization from hexane/ethyl acetate (33:2.5), compound **5h** (99.1 mg, 46%) was obtained as a light brown solid, Mp 179°C, R_f (*n*-hexane/ethyl acetate 1:1) = 0.50.

^1H NMR (300 MHz, $CDCl_3$): δ = 1.57 (s, 9 H), 2.31 (s, 3 H), 2.93 (s, 6 H), 4.714.90 (m, 2 H), 5.76 (s, 1 H), 6.39 (d, *J* = 8.7 Hz, 2 H), 6.57 (d, *J* = 8.7 Hz, 2 H), 7.548.03 (m, 7 H), 8.31 (d, *J* = 8.4 Hz, 1 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 23.0 (CH_3), 28.8 (CH_3), 40.8 (CH_3), 49.9 (CH_2), 51.9 (C_{quat}), 58.0 (CH), 112.4 (CH), 123.9 (CH), 125.2 (CH), 125.6 (C_{quat}), 126.2 (CH), 127.1 (CH), 127.2 (CH), 127.9 (CH), 128.9 (CH), 129.7 (CH), 132.0 (C_{quat}), 132.8 (C_{quat}), 133.8 (C_{quat}), 149.3 (C_{quat}), 170.2 (C_{quat}), 173.0 (C_{quat}). MALDI-TOF-MS (*m/z*): 430.1 ($[M]^+$). IR: $\tilde{\nu}$ [cm^{-1}] = 3,647 (w); 3,283 (w); 3,233 (w); 3,069 (w); 2,972 (w); 2,909 (w); 2,801 (w); 2,309 (w); 1,684 (s); 1,632 (m); 1,618 (s); 1,597 (w); 1,558 (m); 1,456 (w); 1,412 (m); 1,364 (m); 1,350 (w);

1,337 (m); 1,314 (w); 1,273 (w); 1,260 (w); 1,225 (m); 1,192 (w); 1,180 (w); 1,142 (w); 1,053 (w); 1,024 (w); 976 (w); 941 (w); 910 (w); 795 (s); 777 (s); 754 (w); 735 (w); 667 (w). UV/Vis (CH_2Cl_2): λ_{max} (ε [$Lmol^{-1}$ cm^{-1}]) [nm] = 265 (19,000). Fluorescence (CH_2Cl_2): $\lambda_{max,em}$ [nm] = 334, 472. Stokes shift $\Delta\tilde{\nu}$ = 7,800 cm^{-1}. Anal. calcd. for $C_{27}H_{33}N_3O_2$ (431.3): C 75. 14, H 7.71, N 9.74; Found: C 74.88, H 7.67, N 9.46.

N-tert-butyl-2-(4-(dimethylamino)phenyl)-2-(*N*-(1-pyrenylmethyl)acetamido) acetamide (5i)

According to the GP and after chromatography on silica gel (*n*-hexane/ethyl acetate 1:1) and crystallization from hexane/ethyl acetate (45:3.5), compound **5i** (102 mg, 40%) was obtained as a light brown solid, Mp 217–219°C, R_f (*n*-hexane/ethyl acetate 1:1) = 0.20.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.24 (t, *J* = 7.1 Hz, 0.6 H), 1.36 (s, 9 H), 2.02 (s, 0.6 H), 2.10 (s, 3 H), 2.51 (s, 6 H), 4.10 (q, *J* = 7.1 Hz, 0.4 H), 5.245.52 (m, 2 H), 5.57 (s, 1 H), 6.04 (s, 1 H), 6.25 (d, *J* = 8.6 Hz, 2 H), 7.17 (d, *J* = 8.5 Hz, 2 H), 7.748.17 (m, 9 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.3 (CH_3), 21.2 (CH_3), 22.6 (CH_3), 28.9 (CH_3), 40.0 (CH_3), 48.0 (CH_2), 51.7 (C_{quat}), 60.5 (CH_2), 62.6 (CH), 112.1 (CH), 121.8 (C_{quat}), 122.0 (CH), 123.8 (CH), 124.6 (C_{quat}), 124.8 (CH), 125.1 (CH), 125.3 (CH), 126.0 (CH), 126.9 (CH), 127.2 (CH), 127.5 (C_{quat}), 130.2 (CH), 130.7 (C_{quat}), 130.9 (C_{quat}), 131.3 (CH), 131.4 (C_{quat}), 150.1 (C_{quat}), 170.07 (C_{quat}), 172.9 (C_{quat}), 173.0 (C_{quat}). MALDI-TOF-MS (*m*/*z*): 504.2 ([M]$^+$). IR: $\tilde{\nu}$ [cm^{-1}] = 3,289 (w); 3,040 (w); 2,961 (w); 2,893 (w); 2,805 (w); 1,739 (w); 1,670 (m); 1,612 (s); 1,587 (w); 1,547 (m); 1,522 (s); 1,433 (m); 1,414 (m); 1,391 (w); 1,360 (m); 1,339 (w); 1,304 (w); 1,267 (w); 1,254 (w); 1,225 (m); 1,204 (m); 1,167 (m); 1,132 (w); 1,063 (w); 1,032 (w); 980 (w); 934 (w); 843 (s); 812 (m); 797 (m); 710 (s); 640 (w). UV/Vis (CH_2Cl_2): λ_{max} (ε [$Lmol^{-1}$ cm^{-1}]) [nm] = 317 (13,000), 331 (27,000), 347 (36,000). Fluorescence (CH_2Cl_2): $\lambda_{max,em}$ [nm] = 383, 397, 499. Stokes shift $\Delta\tilde{\nu}$ = 2,700 cm^{-1}. Anal. calcd. for $C_{33}H_{35}N_3O_2$ 1/5 $CH_3CO_2C_2H_5$ (505.3 + 17.6): C 77.58, H 7.05, N 8.02; Found: C 77.11, H 7.00, N 8.02.

N-(tert-butyl)-2-(*N*-(4-(dimethylamino) benzyl)acetamido)-2-(1-pyrenyl)acetamide (5j)

According to the GP and after chromatography on silica gel (*n*-hexane/ethyl acetate 1:1) and crystallization from hexane/ethyl acetate (62:4.5), compound **5j** (160 mg, 63%) was obtained as a light brown solid, Mp 202–205°C, R_f (*n*-hexane/ethyl acetate 1:1) = 0.30.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.201.25 (m, 1.2 H), 1.37 (s, 9 H), 2.00 (s, 1.2 H), 2.20 (s, 6 H), 2.21 (s, 3 H), 4.08 (q, *J* = 7.1 Hz, 0.8 H), 4.454.76 (m, 2 H), 5.70 (s, 1 H), 5.70 (d, *J* = 8.5 Hz, 2 H), 6.21 (d, *J* = 8.6 Hz, 2 H), 7.25 (s, 1 H), 7.888.27 (m, 9 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.28 (CH_3), 21.0 (CH_3), 22.9 (CH_3), 28.9 (CH_3), 40.2 (CH_3), 50.2 (CH_2), 52.0 (C_{quat}), 58.3 (CH), 60.5 (CH_2), 111.8 (CH), 123.3 (CH), 124.5 (C_{quat}), 124.7 (C_{quat}), 124.8 (CH), 125.0 (C_{quat}), 125.6 (CH), 126.1 (CH) 126.7 (CH), 127.2 (CH), 127.3 (CH), 127.9 (CH), 128.7 (CH), 129.1 (C_{quat}), 130.8 (C_{quat}), 130.9 (C_{quat}), 131.2 (C_{quat}), 131.8 (C_{quat}), 148.5 (C_{quat}), 170.1 (C_{quat}), 170.4 (C_{quat}), 172.8 (C_{quat}). MALDI-TOF-MS (*m*/*z*): 504.2 ([M]$^+$). IR: $\tilde{\nu}$ [cm^{-1}] = 3,304 (w); 3,040 (w); 2,965 (w); 2,897 (w); 2,884 (w); 2,874 (w); 1,733 (w); 1,684 (m); 1,674 (w); 1,616 (s); 1,549 (m); 1,524 (m); 1,506 (w); 1,468 (w); 1,435 (m); 1423 (m), 1393 (w),1366 (w), 1341 (w), 1314 (w), 1277 (w), 1253 (w), 1225 (m), 1175 (w), 1126 (w), 1,053 (w); 1,034 (w); 980 (w); 972 (w); 943 (w); 910 (w); 845 (s); 812 (w); 799 (m); 758 (w); 710 (w); 681 (w). UV/Vis (CH_2Cl_2): λ_{max} (ε [$Lmol^{-1}$ cm^{-1}]) [nm] = 317 (14,000), 331 (28,000), 348 (38,000). Fluorescence (CH_2Cl_2): $\lambda_{max,em}$ [nm] = 380, 395, 538. Stokes shift $\Delta\tilde{\nu}$ = 2,400 cm^{-1}. Anal. calcd. for $C_{33}H_{35}N_3O_2$ 1/2 $CH_3CO_2C_2H_5$ (505.3 + 44.1): C 76.47, H 7.15, N 7.64; Found: C 76.51, H 7.15, N 8.10.

DATA AVAILABILITY STATEMENT

All datasets generated for this study are included in the article/**Supplementary Material**.

AUTHOR CONTRIBUTIONS

The project was conceptualized by TM for the MSc thesis of MO, who developed the synthetic approach and conducted the photophysical studies and their evaluation. BM performed all DFT and TDDFT calculations and assigned the experimental absorption and emission bands transitions. Based upon the master thesis of MO, the manuscript was written and corrected by TM and BM.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fchem.2019.00717/full#supplementary-material

Supplementary Information contains the optimization of the synthesis of compound **5a**, ^{1}H and ^{13}C NMR spectra of compounds **5**, the absorption and emission spectra of compounds **5**, the Lippert-Mataga analysis of dyad **5a** and the data and evaluation of the DFT and TDDFT calculations on the *syn*- and *anti*-structures **5a**, **5g**, and **5i**.

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