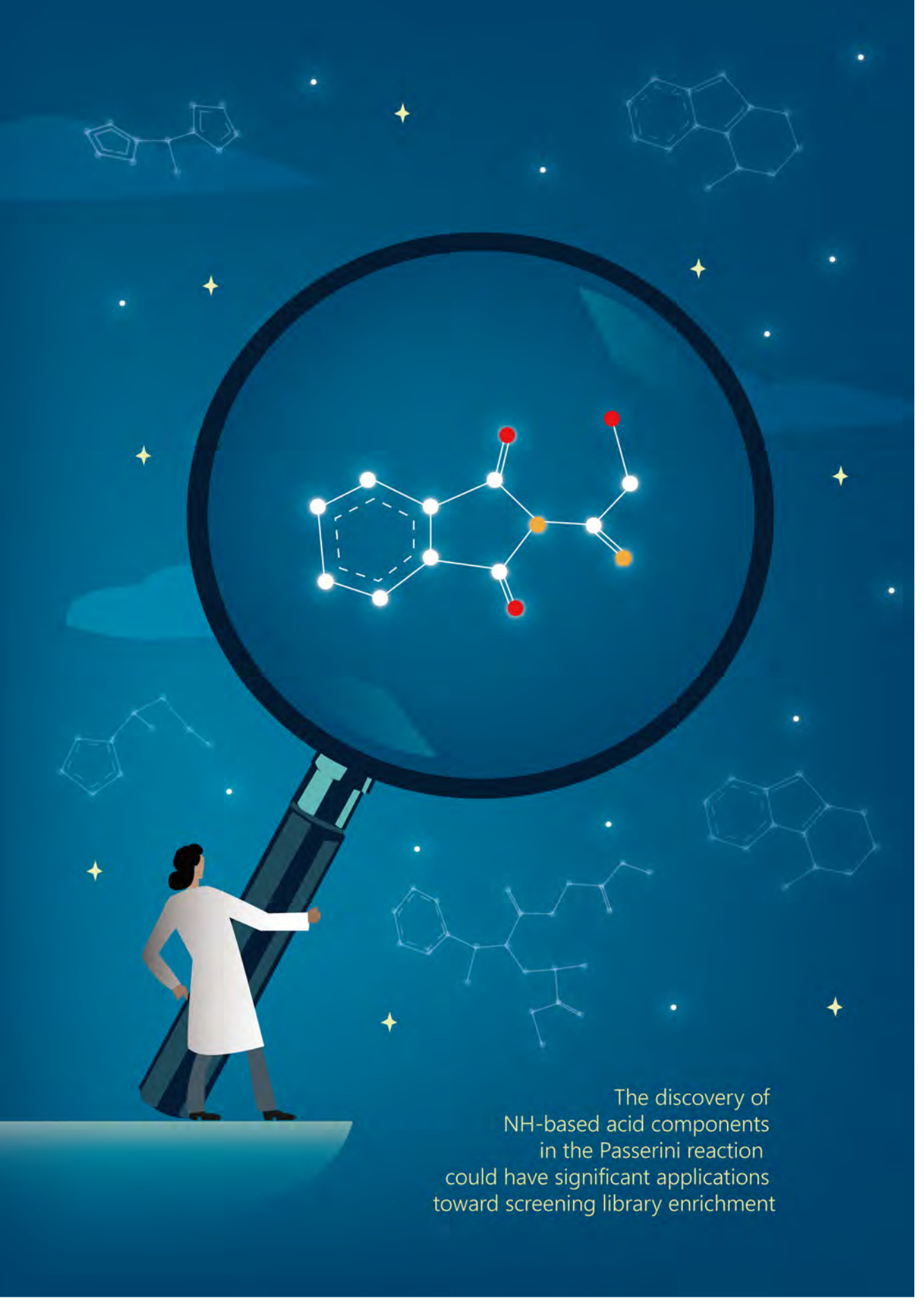


The discovery of
NH-based acid components
in the Passerini reaction
could have significant applications
toward screening library enrichment

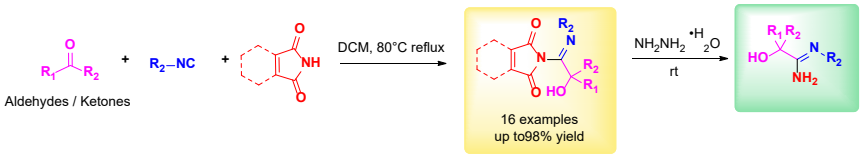
CHAPTER 4

Phthalimide as the Acid Component in the Passerini Reaction

Jingyao Li, Alexander Dömling

In prep. for submission

Abstract



Multicomponent reactions and in particular the Passerini reaction, are considered efficient tools for synthesizing drug-like molecules and assembling compound libraries. In the case of the Passerini reaction, however, the alternatives for the essential carboxylic acid component remain a limiting factor. Here we focus on the phthalimide moiety and its derivatives in the Passerini reaction and their potential for the synthesis of diverse and complex molecules. The phthalimide moiety is an attractive building block due to the oxidative stability, heat retardant and solvent resistant properties. Our approach provides a fresh orientation of MCRs by utilizing NH-based acid components and fulfilling the constant demand for the development of novel scaffolds.

Introduction

MCRs (multicomponent reactions) are chemical transformations that can efficiently generate a single multi-functional product by incorporating three or more reactants with almost all of their atoms and are thus regarded as a considerable toolbox to expand molecular diversity and complexity in synthetic and medicinal chemistry[1-3]. Among them, Passerini (**Figure 1a**)[4] and Ugi (**Figure 1b**)[5] MCRs have experienced rapid growth with applications in diverse compound libraries and functionalized scaffolds, owing to the ready access of a large number of starting materials. Both reactions share a similar mechanism, which begins with the activation of the aldehyde by the carboxylic acid component. However, the utilization of carboxylic acids could also be considered as a limitation of the reactions due to a finite number of readily available variations.

In 2006, El Kaim and coworkers reported the use of O-arylative compounds as a replacement of carboxylic acids in both Passerini and Ugi reactions to access α-aryloxy-amides[6] as well as O-and N-arylamides[7] (**Figure 1c**). Subsequently, the use of other starting materials instead of carboxylic acids has been reported (**Figure 1A**). A direct alkylative Passerini reaction was reported using free aliphatic alcohols to obtain the corresponding α-alkoxyl amide products (**Figure 1d**)[8]. In this case, however, the requirement for α,β-unsaturated aldehydes, and tert-butyl isocyanide, in addition to the use of an In catalyst, limited the application of this methodology. Later on, O-silylative[9] (**Figure 1e**) and O-phosphinative[10] (**Figure 1f**) Passerini reactions were developed for the synthesis of α-siloxyamides and α-(phosphinyloxy)amides by replacing the carboxylic acid with triphenylsilanol and phenylphosphinic acid, respectively. Our group also reported N-hydroxamic acids as an acid component in Passerini reaction toward α-aminoxy-amides (**Figure 1g**)[11]. In 2018, Saya et al reported the use of hexafluoroisopropanol as an acid component in the Passerini reaction, synthesizing β-amino alcohols via a two-step one-pot approach (**Figure 1h**)[12]. To date, all carboxylic acid replacements in the Passerini reaction are OH-based acid bioisosteres. Thus, the discovery of non-OH-based acid components in the Passerini reaction is unstudied and of great interest.

Phthalimide, a bicyclic non-aromatic nitrogen heterocycle, has an acidic pKa value of 8.3 and is considered a perfect carboxylic acid bioisostere. Due to its lipophilic and neutral properties, phthalimide and its derivatives can easily cross biological membranes and therefore, exhibits enormous pharmaceutical potential[13]. A large number of phthalimide subunit-containing compounds have been designed and developed as anti-tumor[14-16],

anti-inflammatory[17-18], anti-Alzheimer (AD)[19], antipsychotic[20], antimicrobial[21], anticonvulsant[22], anxiolytic[23], and anti-HIV agents[24]. Several of these compounds have reached the market for the treatment of multiple myeloma (Thalidomide)[25], psoriasis (Apremilast)[26], rheumatoid arthritis, and shock septic syndrome (LASSBio-468)[27]. In addition to its abundant medicinal applications, the phthalimide moiety also plays an important role in synthetic chemistry and is considered as a precursor for the synthesis of amines[28] and anthranilic acids[29].

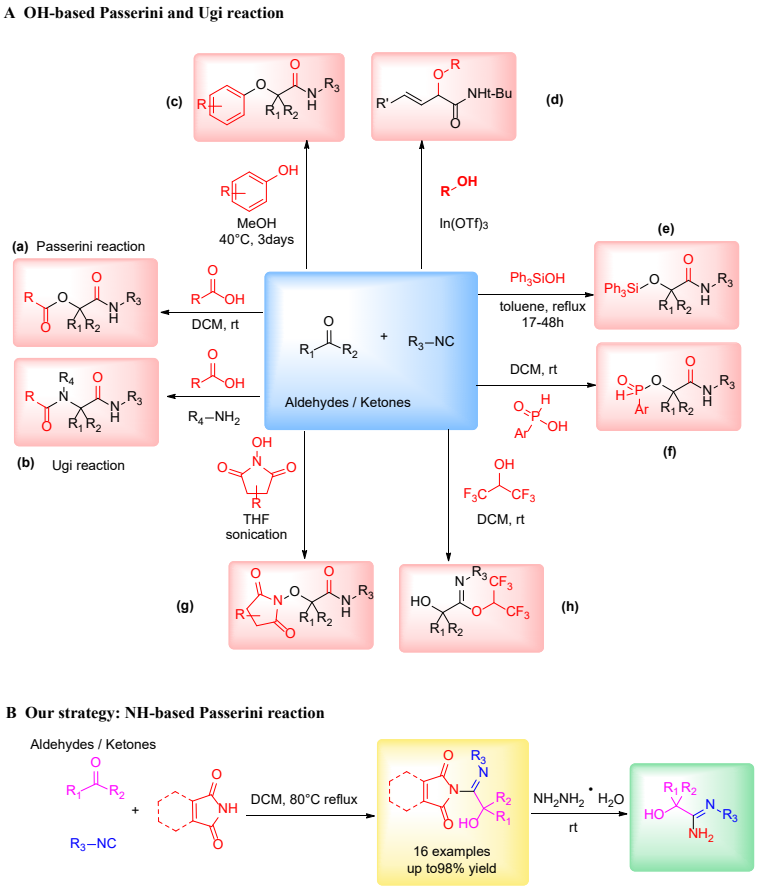
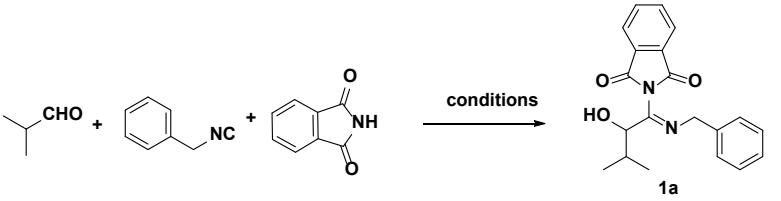


Figure 1. Different acid components in the Passerini reaction.

On the other hand, the acidic properties of phthalimide, remain less explored. .The phthalimide moiety could be introduced in MCR scaffolds to form multi-substituted compounds and here, we explore the potential of phthalimide as the acid component in the Passerini reaction.

Result and Discussion

Table 1. Optimization of reaction conditions



Entry	Solvent	Time	Base	Temp	Yield (%)[a]
1	DCM	2 days	-	rt	20%
2	DCM	overnight	-	55°C	43%
3	THF	overnight	-	55°C	40%
4	DCM:THF(1:1)	overnight	-	55°C	35%
5	MeOH	overnight	-	55°C	trace
6	DCM	overnight	Et_3N	55°C	ND
7	THF	overnight	Et_3N	55°C	ND
8	DCM:DMF(9:1)	overnight	Et_3N	55°C	ND
9	Dioxane	overnight	Et_3N	55°C	ND
10	DCM	4h	-	80°C	90%
11	THF	4h	-	80°C	52%
12	DCM:DMF(1:1)	4h	-	80°C	81%
13	DCM:DMF(9:1)	4h	-	80°C	83%
14	Dioxane	4h	-	80°C	77%

[a] Isolated yields.

Initially, to develop our strategy, we performed the optimization of reaction conditions. For this aim, isobutyraldehyde (1.0 equiv), benzyl isocyanide (1.0 equiv), and phthalimide (1.0 equiv) were utilized as starting materials (**Table 1**). To the best of our knowledge, aprotic solvents are more preferable than protic solvents in Passerini type reactions, and among them, DCM is the most commonly used solvent. Therefore, we started the investigation by using DCM at room temperature. However, , phthalimide has poor solubility in DCM and the starting materials didn't fully convert even after two-days reaction, resulting in only 20% yield (**Table 1**, **entry 1**). Thus, the solubility of phthalimide is significantly hindering the reaction. . We hypothesized that by increasing the temperature of the reaction, the solubility of phthalimide could improve and as a

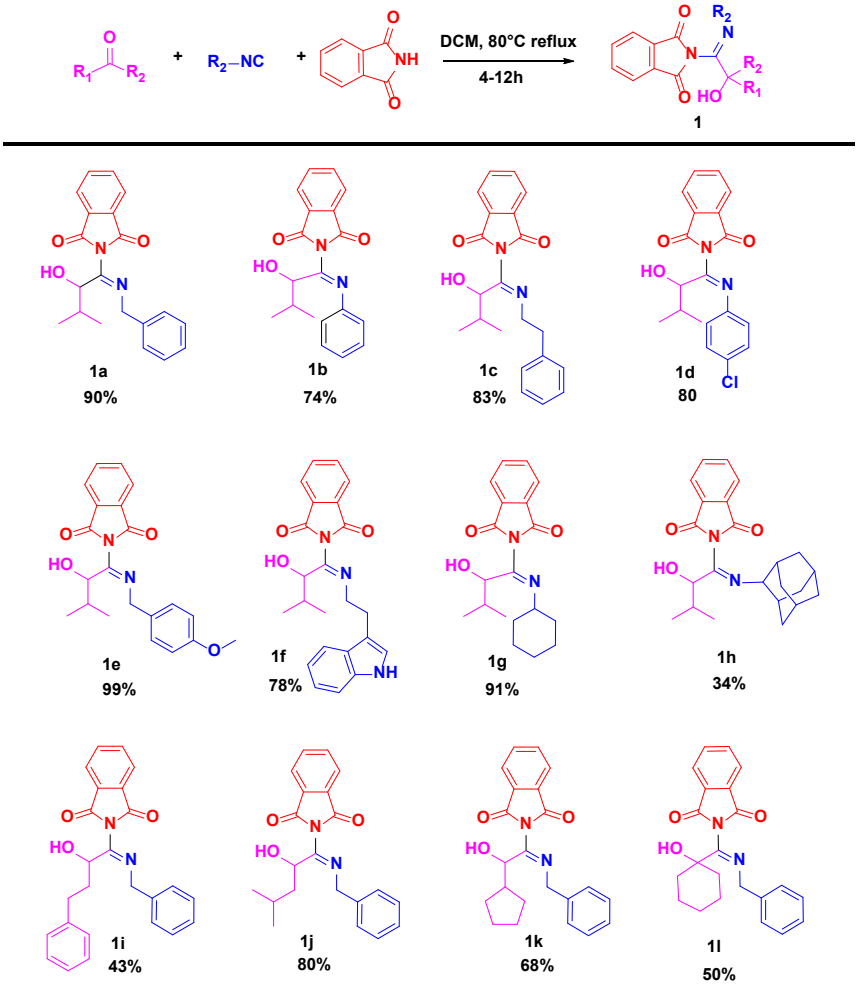
consequence, the reaction would be faster.., Indeed, by performing the reaction at 55°C, the yield increased to 43% (**Table 1**, **entry 2**). Moreover, the use of different solventS could also be a factor that could improve the reaction. Although THF and MeOH, improved the solubility of phthalimide, the yields decreased (**Table 1**, **entry 3-5**). Furthermore, the use of organic bases could form ions with the phthalimide due to its acidic properties and possibly help it dissolve in the organic solvents as well. However, the addition of trimethylamine failed to boost the reaction and on the contrary hindered the formation of the product (**Table 1**, **entry 6-9**). Thus, after all the above-mentioned attempts, we concluded that the major factor to improve the yield of the reaction, is the temperature. We returned to our initial reaction conditions and increased the temperature to 80°C. To our delight, the increased temperature not only provided excellent yields, but also accelerated the reaction time to 4 hours (**Table 1**, **entry 10-14**). Next, we tested different solvent systems, aiming to improve the solubility of phthalimide. Reactions in THF and dioxane led to lower yields, 52% and 77% respectively (**Table 1**, **entry 11** and **14**). The use of solvent mixtures (DCM and DMF) led to good yields of 81% and 83% (**Table 1**, **entry 12** and **13**) however pure DCM as solvent provided the best yield of 90% (**Table1**, **entry 10**).

With this optimized condition in hand, our next aim was to establish the substrate scope, using diverse oxo component and isocyanides. Initially, we used various aliphatic and aromatic isocyanides. Most of the aromatic isocyanide components resulted in excellent yields from 74% to 99% (**1a**-**1f**). Mono-substituted aromatic isocyanides (p-chloro, p-methoxy) led to better yields of 80% and 99% respectively, compared to non-substituted aromatic isocyanides (**1a**, **1b**). Additionally, 2-(2-Phenyl-1H-indole-3-yl) ethyl isocyanide (**1f**) with a 1H-indole substitution led to a good yield of 78% as well. As aliphatic isocyanides, cyclohexene isocyanide and 2-adamantyl isocyanide, were utilized in this reaction and resulted in moderate to good yields, 91% and 34% respectively. In contrast to the aromatic isocyanides, the outcome for aliphatic isocyanides, depends on their substitutions. Steric hindrance of the bulkyadamantly- group might be the main reason for the low yield of **1h**.

Next, we turned our focus on the aldehyde component. In this case, aromatic aldehydes decreased the product yield (**1i**), whereas both the linear and cyclic aliphatic aldehydes displayed moderate to good yields, 80% (**1j**) and 68% (**1k**), respectively. It is noteworthy that an example with a ketone was also successful, resulting in a 50% yield (**1l**). The

overall scope of aldehyde and isocyanide components assembled a compound library of high complexity and diversity, and revealed the prominent availability and excellent tolerance of the present strategy.

Scheme 1. Substrate Scope of the Phthalimide conducted Passerini Products (**1**)[a]

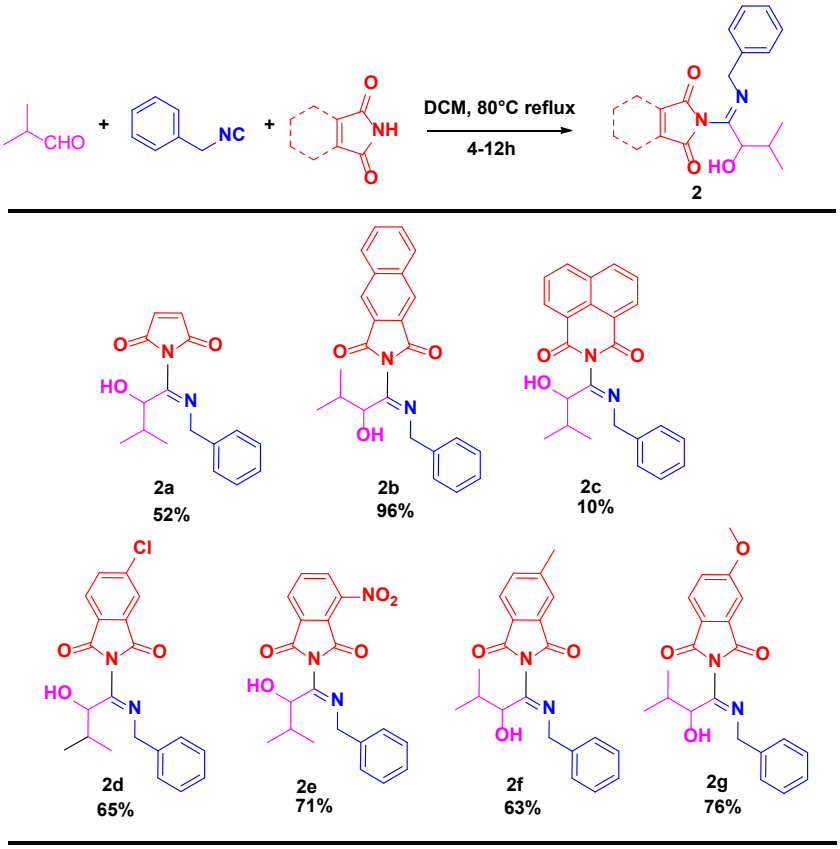


[a] Isolated yield

Besides the use of phthalimide, we envisioned that N-formylformamide containing conjugated cyclic compounds, with low pKa values, could be treated as acid bioisosteres and used in the present strategy as well (**Scheme 2**). The exploration started with 1H-pyrrole-2,5-dione (**2a**), which lacks one phenyl ring compared with phthalimide. The lack of one phenyl ring reduced the acidic properties and led to a decreased yield

of 52%. On the other hand, addition of phenyl rings on different positions resulted in diverse yields. 1H-Benz[f]isoindole-1,3(2H)-dione (**2b**), which remained the basic 5-membered N-formylformamide cyclic scaffold of phthalimide, reacted with high yield (96%), whereas 1H-Benzo[de]isoquinoline-1,3(2H)-dione (**2c**), containing a 6-membered N-formylformamide cyclic scaffold, resulted in only 10% yield. Furthermore, the effect of diverse substitutions was explored as well. Substituents on positions 4 and 5, including halogens (**2d**), nitro (**2e**), methoxyl (**2f**) and methyl (**2g**) substituents were well tolerated with moderate to good yields. Overall, the successful strategy using phthalimide derivatives with different substituents in the Passerini reaction produces a diverse library of products.

Scheme 2. Substrate Scope of Phthalimide Derivatives (**2**)[a]

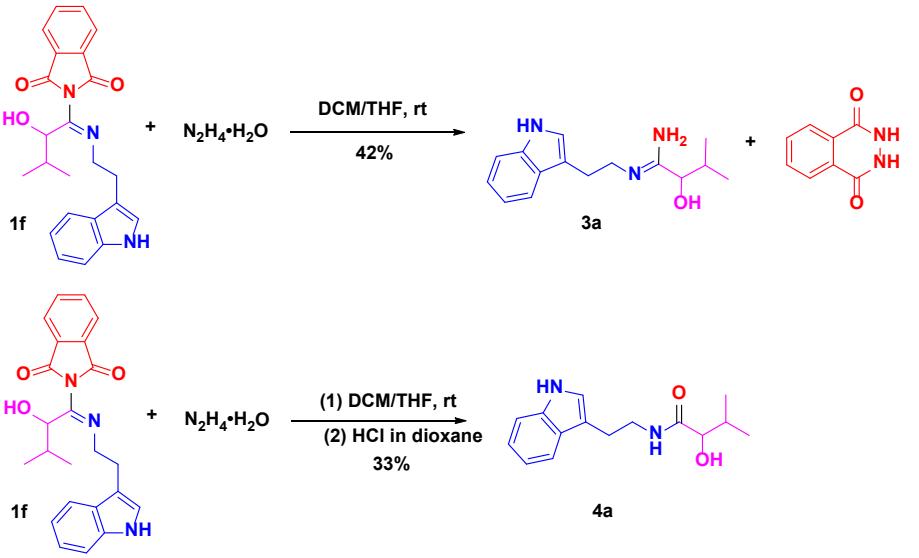


[a] Isolated yield

As an application of this methodology, we next investigated the cleavage of phthalimide toward the hydroxy imidines which are important intermediates for the synthesis of

bioactive heterocycles (**Scheme 3**). We first conducted the Passerine reaction in 1mL DCM to the formation of 2-(1-((2-(1H-indol-3-yl)ethyl)imino)-2-hydroxy-3-methylbutyl) isoindoline-1,3-dione (**1f**). The reaction was monitored by TLC and upon completion, 1mL THF was added to the reaction mixture, followed by hydrazine. The reaction was stirred for 1 h at room temperature, forming the imidine (**3a**). However, when HCl in dioxane was added to the reaction mixture, the expected HCl salt was not observed, and unexpectedly amide (**4a**) was formed by oxidation. All these reactions were conducted in a one-pot manner, without any column chromatography for the intermediates.

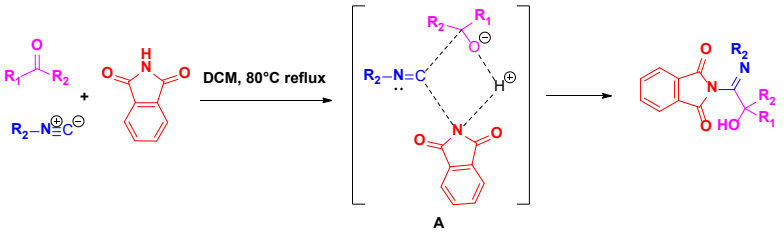
Scheme 3. Cleavage of Phthalimide to the Synthesis of β-Amidine Alcohol (**3**) [a]



[a] Isolated yield

Since several Passerini products are detected in almost quantitive yields, we propose that the reaction mechanism is more likely in the foward Passerini-type reaction (scheme 4). The first step is the activation of the aldehyde by the NH moiety of phthalimide primarily, and then nucleophilic attack of the isocyanide to the carbonyl group of aldehyde occurs, and subsequently, leads to the formation of a cyclic intermediate **A**. The hydrogen of phthalimide rearranges to the aldehyde oxygen and gives the corresponding alcohol.

Scheme 4. Predicted Mechanism of the Passerini Reaction



Conclusion

In conclusion, we have shown a unique application of the phthalimide moiety, as a replacement for the carboxylic acid component in the Passerini reaction. The methodology was examined by a small library synthesis, exhibiting good tolerance for both aromatic and aliphatic building blocks. Product diversity can be achieved through all components. Subsequent cleavage of phthalimide allows the straightforward synthesis of β-hydroxy amidines and β-hydroxy amides which otherwise are difficult to access. The discovery of this approach could have significant applications toward screening library enrichment.

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Experimental section

Experimental procedures

Procedure A: General procedure for the synthesis of compounds 1 and 2:

A 5 mL microwave vial equipped with a magnetic stirring bar was charged with aldehyde (1.0 mmol), phthalimide or its derivative (1.0 mmol) and isocyanide (1.0 mmol) in 2mL DCM at room temperature. The vial was sealed with a cap containing a septum and subjected to metal block heating at 80 °C till completion of reaction (reaction monitored by TLC). The solvent was removed under reduced pressure and residue was purified by silica gel flash chromatography using EtOAc–hexane as eluent on to afford the titled product.

Procedure B: General procedure for the synthesis of compound 3:

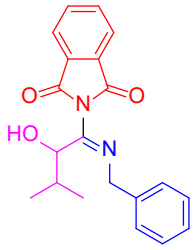
A 5 mL microwave vial equipped with a magnetic stirring bar was charged with an aldehyde (1.0 mmol), phthalimide or its derivative (1.0 mmol) and isocyanide (1.0 mmol) in 2mL DCM at room temperature. The vial was sealed with a cap containing a septum and subjected to metal block heating at 80 °C till completion of reaction (reaction monitored by TLC). The reaction was cooled to room temperature. 2mL THF and $NH_2NH_2{\cdot}H_2O$ (1.05 mmol) were added to the reaction, sequentially. After 1h, the reaction mixture was filtered and the filtrate was concentrated under reduced pressure. The residue was purified by silica gel flash chromatography using DCM-MeOH as eluent on to afford the titled product.

Procedure C: General procedure for the synthesis of compound 4:

A 5 mL microwave vial equipped with a magnetic stirring bar was charged with an aldehyde (1.0 mmol), phthalimide or its derivative (1.0 mmol) and isocyanide (1.0 mmol) in DCM at room temperature. The vial was sealed with a cap containing a septum and subjected to metal block heating at 80 °C till completion of reaction (reaction monitored by TLC). The reaction was cooled to room temperature. 2mL THF and $NH_2NH_2{\cdot}H_2O$(1.05 mmol) were added to the reaction, sequentially. After 1h, , the reaction mixture was filtered. In the filtrate, 4N HCl in dioxane (1mL) was added reacted for 10 min. The solvent was removed under reduced pressure and residue was purified by silica gel flash chromatography using DCM-MeOH as eluent on to afford the titled product.

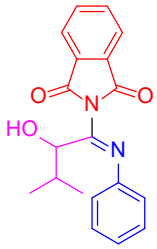
Characterization data

2-(1-(benzylimino)-2-hydroxy-3-methylbutyl)isoindoline-1,3-dione (1a)



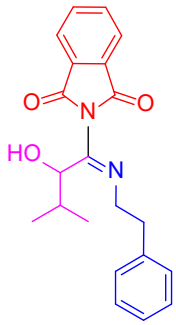
Synthesized according to procedure A from 1 mmol reaction as colorless liquid, yield: 303 mg (90 %); ^{1}H NMR (500 MHz, Chloroform-d) δ 7.91 (dd, *J* = 5.5, 3.1 Hz, 2H), 7.78 (dd, *J* = 5.5, 3.0 Hz, 2H), 7.34 – 7.26 (m, 4H), 7.25 – 7.17 (m, 1H), 4.68 (dd, *J* = 16.0, 1.8 Hz, 1H), 4.61 (dt, *J* = 3.0, 1.5 Hz, 1H), 4.50 (dd, *J* = 15.9, 1.3 Hz, 1H), 1.93 (pd, *J* = 6.8, 2.7 Hz, 1H), 1.09 (d, *J* = 6.9 Hz, 3H), 0.90 (d, *J* = 6.8 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 151.7, 138.2, 135.1, 131.4, 128.5, 127.8, 127.1, 124.3, 75.7, 54.8, 31.4, 20.2, 15.1. MS (ESI) m/z calculated for $C_{20}H_{20}N_2O_3$ $[M+H]^+$: 337.16; found $[M+H]^+$: 337.35.

2-(2-hydroxy-3-methyl-1-(phenylimino)butyl)isoindoline-1,3-dione (1b)



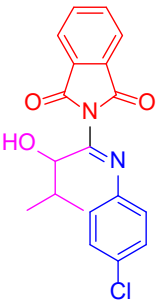
Synthesized according to procedure A from 1 mmol reaction as colorless liquid, yield: 237 mg (74 %); ^{1}H NMR (500 MHz, Chloroform-d) δ 7.83 – 7.75 (m, 2H), 7.74 – 7.66 (m, 2H), 7.24 – 7.13 (m, 2H), 7.05 – 6.95 (m, 1H), 6.88 – 6.80 (m, 2H), 4.68 (d, *J* = 2.9 Hz, 1H), 2.14 – 1.96 (m, 1H), 1.15 (d, *J* = 6.9 Hz, 3H), 1.02 (d, *J* = 6.8 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 152.3, 146.5, 134.8, 131.1, 128.9, 125.1, 124.1, 119.4, 76.3, 31.2, 20.2, 15.1. MS (ESI) m/z calculated for $C_{19}H_{18}N_2O_3$ $[M+H]^+$: 323.14; found $[M+H]^+$: 323.31.

2-(2-hydroxy-3-methyl-1-(phenethylimino)butyl)isoindoline-1,3-dione (1c)



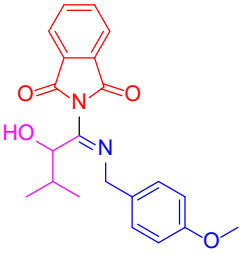
Synthesized according to procedure A from 1 mmol reaction as colorless liquid, yield: 292 mg (83 %);^{1}H NMR (500 MHz, Chloroform-d) δ 7.89 (dd, *J* = 5.5, 3.0 Hz, 2H), 7.79 (dd, *J* = 5.5, 3.0 Hz, 2H), 7.30 – 7.23 (m, 2H), 7.20 – 7.11 (m, 3H), 3.89 (d, *J* = 5.2 Hz, 1H), 3.77 – 3.63 (m, 1H), 3.60 – 3.47 (m, 1H), 3.13 – 3.03 (m, 1H), 3.02 – 2.90 (m, 1H), 1.92 – 1.74 (m, 1H), 1.06 (d, *J* = 6.9 Hz, 3H), 0.85 (d, *J* = 6.8 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 150.7, 139.5, 135.0, 131.4, 128.8, 128.5, 126.3, 124.3, 75.4, 52.8, 36.8, 31.3, 20.1, 14.9. MS (ESI) m/z calculated for $C_{21}H_{22}N_2O_3$ $[M+H]^+$: 351.17; found $[M+H]^+$: 351.38.

2-(1-((4-chlorophenyl)imino)-2-hydroxy-3-methylbutyl)isoindoline-1,3-dione (1d)



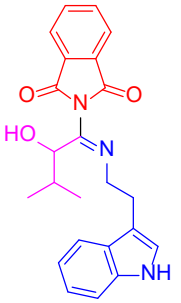
Synthesized according to procedure A from 1 mmol reaction as colorless liquid, yield: 284 mg (80 %); ^{1}H NMR (500 MHz, Chloroform-d) δ 7.92 – 7.78 (m, 2H), 7.77 – 7.68 (m, 2H), 7.20 – 7.09 (m, 2H), 6.85 – 6.73 (m, 2H), 4.68 (d, *J* = 3.0 Hz, 1H), 2.10 – 1.94 (m, 1H), 1.14 (d, *J* = 6.9 Hz, 3H), 1.00 (d, *J* = 6.8 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 153.1, 145.1, 135.0, 131.0, 130.6, 129.1, 124.3, 120.9, 76.3, 31.3, 20.1, 15.1. MS (ESI) m/z calculated for $C_{19}H_{17}ClN_2O_3$ $[M+H]^+$: 357.10; found $[M+H]^+$: 357.28.

2-(2-hydroxy-1-((4-methoxybenzyl)imino)-3-methylbutyl)isoindoline-1,3-dione (1e)



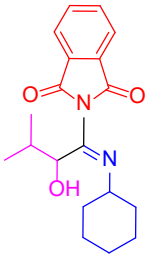
Synthesized according to procedure A from 1 mmol reaction as colorless liquid, yield: 362mg (99 %); ^{1}H NMR (500 MHz, Chloroform-d) δ 7.91 (dd, *J* = 5.5, 3.0 Hz, 2H), 7.80 (dd, *J* = 5.5, 3.1 Hz, 2H), 7.21 (d, *J* = 8.6 Hz, 2H), 6.83 (d, *J* = 8.7 Hz, 2H), 4.67 – 4.55 (m, 2H), 4.45 (d, *J* = 15.4 Hz, 1H), 3.75 (s, 3H), 1.92 (pd, *J* = 6.8, 2.6 Hz, 1H), 1.08 (d, *J* = 7.0 Hz, 3H), 0.90 (d, *J* = 6.8 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 158.7, 151.2, 135.0, 131.4, 130.3, 128.9, 124.3, 113.9, 75.6, 55.2, 54.3, 31.3, 20.1, 15.1. MS (ESI) m/z calculated for $C_{21}H_{22}N_2O_4$ $[M+H]^+$: 367.17; found $[M+H]^+$: 367.33.

2-(1-((2-(1H-indol-3-yl)ethyl)imino)-2-hydroxy-3-methylbutyl)isoindoline-1,3-dione (1f)



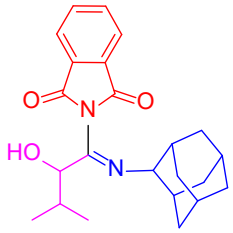
Synthesized according to procedure A from 1 mmol reaction as colorless liquid, yield: 305 mg (78 %); ^{1}H NMR (500 MHz, Chloroform-d) δ 8.45 – 8.33 (m, 1H), 7.85 – 7.69 (m, 2H), 7.68 – 7.61 (m, 2H), 7.45 (d, *J* = 8.0 Hz, 1H), 7.25 (d, *J* = 8.2 Hz, 1H), 7.04 (ddd, *J* = 8.1, 6.9, 1.1 Hz, 1H), 6.93 (d, *J* = 2.3 Hz, 1H), 6.87 (ddd, *J* = 8.0, 7.0, 1.0 Hz, 1H), 4.56 – 4.49 (m, 1H), 3.86 – 3.76 (m, 1H), 3.70 – 3.60 (m, 1H), 3.23 – 3.12 (m, 1H), 3.11 – 3.01 (m, 1H), 1.85 (pd, *J* = 6.8, 2.7 Hz, 1H), 1.06 (d, *J* = 6.9 Hz, 3H), 0.87 (d, *J* = 6.8 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 150.6, 136.4, 134.8, 131.2, 127.3, 124.1, 122.6, 121.8, 119.1, 118.5, 113.1, 111.3, 75.5, 51.8, 31.3, 26.3, 20.2, 15.1. MS (ESI) m/z calculated for $C_{23}H_{23}N_3O_3$ $[M+H]^+$: 390.18; found $[M+H]^+$: 390.34

2-(1-(cyclohexylimino)-2-hydroxy-3-methylbutyl)isoindoline-1,3-dione (1g)



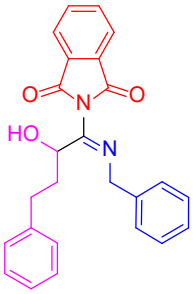
Synthesized according to procedure A from 1 mmol reaction as colorless liquid, yield: 300 mg (91 %); ^{1}H NMR (500 MHz, Chloroform-d) δ 7.96 (dd, *J* = 5.5, 3.1 Hz, 2H), 7.87 (dd, *J* = 5.6, 3.1 Hz, 2H), 4.38 (d, *J* = 2.6 Hz, 1H), 3.43 – 3.16 (m, 1H), 1.91 – 1.82 (m, 2H), 1.82 – 1.68 (m, 2H), 1.65 – 1.46 (m, 4H), 1.30 – 1.22 (m, 3H), 1.06 (d, *J* = 6.9 Hz, 3H), 0.87 (d, *J* = 6.8 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 147.8, 134.8, 131.4, 124.1, 75.5, 59.5, 33.5, 32.9, 30.7, 25.5, 24.0, 23.9, 20.1, 14.7. MS (ESI) m/z calculated for $C_{19}H_{24}N_2O_3$ $[M+H]^+$: 329.19; found $[M+H]^+$: 329.36

2-(-1-((-adamantan-2-yl)imino)-2-hydroxy-3-methylbutyl)isoindoline-1,3-dione (1h)



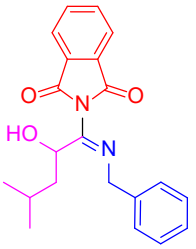
Synthesized according to procedure A from 1 mmol reaction as colorless liquid, yield: 131 mg (34 %); ^{1}H NMR (500 MHz, Chloroform-d) δ 7.91 (dd, *J* = 5.5, 3.1 Hz, 2H), 7.82 (dd, *J* = 5.5, 3.0 Hz, 2H), 4.41 (d, *J* = 2.5 Hz, 1H), 2.41 – 2.28 (m, 2H), 1.96 – 1.89 (m, 2H), 1.88 – 1.82 (m, 3H), 1.81 – 1.77 (m, 2H), 1.76 – 1.73 (m, 2H), 1.69 – 1.64 (m, 1H), 1.63 – 1.57 (m, 3H), 1.56 – 1.52 (m, 1H), 1.06 (d, *J* = 6.9 Hz, 3H), 0.86 (d, *J* = 6.7 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 175.5, 168.4, 147.1, 134.8, 131.4, 124.2, 75.7, 64.7, 52.8, 37.9, 37.0, 36.9, 34.4, 33.5, 31.9, 31.8, 30.8, 27.9, 27.2, 20.2, 14.6. MS (ESI) m/z calculated for $C_{23}H_{28}N_2O_3$ $[M+H]^+$: 381.22; found $[M+H]^+$: 381.41

2-(1-(benzylimino)-2-hydroxy-4-phenylbutyl)isoindoline-1,3-dione (1i)



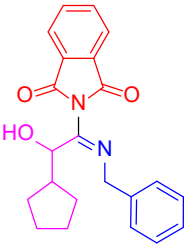
Synthesized according to procedure A from 1 mmol reaction as colorless liquid, yield: 173 mg (43 %);^{1}H NMR (500 MHz, Chloroform-d) δ 7.96 (dd, *J* = 5.5, 3.1 Hz, 1H), 7.90 (dd, *J* = 5.4, 3.1 Hz, 1H), 7.85 (dd, *J* = 5.5, 3.1 Hz, 1H), 7.79 (dd, *J* = 5.5, 3.0 Hz, 1H), 7.43 – 7.32 (m, 4H), 7.31 – 7.14 (m, 6H), 4.85 – 4.74 (m, 1H), 4.72 – 4.64 (m, 1H), 4.61 – 4.46 (m, 1H), 4.20 – 3.79 (m, 1H), 3.04 – 2.62 (m, 2H), 2.19 – 2.03 (m, 1H), 1.99 – 1.85 (m, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 151.6, 141.8, 137.9, 135.0, 134.3, 132.7, 131.4, 128.5, 128.5, 128.4, 127.8, 127.2, 125.9, 124.3, 123.6, 71.4, 54.9, 36.2, 31.1. MS (ESI) m/z calculated for $C_{25}H_{22}N_2O_3$ $[M+H]^+$: 399.17; found $[M+H]^+$: 399.37

2-(1-(benzylimino)-2-hydroxy-4-methylpentyl)isoindoline-1,3-dione (1j)



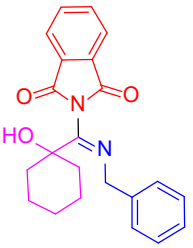
Synthesized according to procedure A from 1 mmol reaction as colorless liquid, yield: 280 mg (80 %); ^{1}H NMR (500 MHz, Chloroform-d) δ 7.93 (dd, *J* = 5.5, 3.1 Hz, 2H), 7.80 (dd, *J* = 5.5, 3.0 Hz, 2H), 7.34 – 7.27 (m, 4H), 7.26 – 7.20 (m, 1H), 4.75 – 4.68 (m, 1H), 4.62 (dd, *J* = 15.9, 1.7 Hz, 1H), 4.50 (dd, *J* = 15.8, 1.3 Hz, 1H), 2.06 – 1.89 (m, 1H), 1.63 – 1.55 (m, 1H), 1.46 – 1.35 (m, 1H), 0.92 (s, 3H), 0.91 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 152.3, 138.1, 135.0, 131.4, 128.5, 127.8, 127.2, 124.3, 70.5, 54.9, 43.5, 24.7, 23.7, 21.4. ppm. MS (ESI) m/z calculated for $C_{21}H_{22}N_2O_3$ $[M+H]^+$: 351.17; found $[M+H]^+$: 351.36

2-(1-(benzylimino)-2-cyclopentyl-2-hydroxyethyl)isoindoline-1,3-dione (1k)



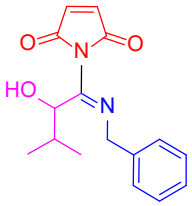
Synthesized according to procedure A from 1 mmol reaction as colorless liquid, yield: 245 mg (68 %); ^{1}H NMR (500 MHz, Chloroform-d) δ 7.95 (dd, *J* = 5.5, 3.1 Hz, 2H), 7.83 (dd, *J* = 5.5, 3.0 Hz, 2H), 7.36 – 7.30 (m, 4H), 7.28 – 7.23 (m, 1H), 4.75 – 4.71 (m, 1H), 4.68 (dd, *J* = 15.9, 1.7 Hz, 1H), 4.53 (dd, *J* = 15.9, 1.2 Hz, 1H), 4.15 – 3.68 (m, 1H), 2.21 – 2.09 (m, 1H), 1.80 – 1.70 (m, 1H), 1.70 – 1.59 (m, 4H), 1.57 – 1.43 (m, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 151.9, 138.2, 135.1, 131.4, 128.5, 127.8, 127.1, 124.3, 73.7, 54.7, 42.7, 29.5, 26.0, 25.9.ppm. MS (ESI) m/z calculated for $C_{22}H_{22}N_2O_3$ $[M+H]^+$: 363.17; found $[M+H]^+$: 363.34

2-((benzylimino)(1-hydroxycyclohexyl)methyl)isoindoline-1,3-dione (1l)



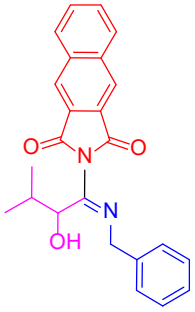
Synthesized according to procedure A from 1 mmol reaction as colorless liquid, yield: 180 mg (50 %); ^{1}H NMR (500 MHz, Chloroform-d) δ 7.92 (dd, *J* = 5.5, 3.1 Hz, 2H), 7.80 (dd, *J* = 5.5, 3.0 Hz, 2H), 7.36 – 7.27 (m, 4H), 7.26 – 7.20 (m, 1H), 4.48 (s, 2H), 1.89 – 1.79 (m, 4H), 1.75 – 1.58 (m, 6H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 166.5, 155.5, 137.9, 134.7, 134.3, 131.6, 128.4, 127.7, 127.1, 124.1, 123.6, 75.8, 55.0, 35.5, 25.3, 21.4. MS (ESI) m/z calculated for $C_{22}H_{22}N_2O_3$ $[M+H]^+$: 363.17; found $[M+H]^+$: 363.36

1-(1-(benzylimino)-2-hydroxy-3-methylbutyl)-1H-pyrrole-2,5-dione (2a)



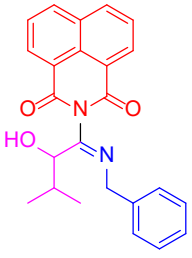
Synthesized according to procedure A from 1 mmol reaction as colorless liquid, yield: 150 mg (52 %);^{1}H NMR (500 MHz, Chloroform-d) δ 7.37 – 7.31 (m, 2H), 7.30 – 7.24 (m, 3H), 6.81 (s, 2H), 4.61 (dd, *J* = 16.0, 1.7 Hz, 1H), 4.52 – 4.46 (m, 1H), 4.42 (dd, *J* = 16.0, 1.3 Hz, 1H), 3.88 – 3.72 (m, 1H), 1.87 – 1.75 (m, 1H), 1.07 (d, *J* = 6.9 Hz, 3H), 0.84 (d, *J* = 6.8 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 150.6, 138.0, 134.8, 128.5, 127.7, 127.2, 75.3, 54.6, 31.5, 20.0, 15.0. ppm. MS (ESI) m/z calculated for $C_{16}H_{18}N_2O_3$ $[M+H]^+$: 287.14; found $[M+H]^+$: 287.33

2-(1-(benzylimino)-2-hydroxy-3-methylbutyl)-1H-benzo[f]isoindole-1,3(2H)-dione (2b)



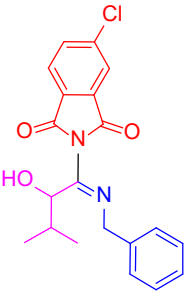
Synthesized according to procedure A from 1 mmol reaction as colorless liquid, yield: 372 mg (96 %); ^{1}H NMR (500 MHz, Chloroform-d) δ 8.39 (s, 2H), 8.03 (dd, *J* = 6.2, 3.3 Hz, 2H), 7.70 (dd, *J* = 6.3, 3.3 Hz, 2H), 7.35 – 7.11 (m, 6H), 4.76 – 4.65 (m, 2H), 4.56 (dd, *J* = 16.4, 1.5 Hz, 1H), 2.12 – 1.91 (m, 1H), 1.12 (d, *J* = 6.9 Hz, 3H), 0.97 (d, *J* = 6.8 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 152.1, 138.3, 135.7, 130.5, 129.9, 128.5, 127.8, 127.1, 126.7, 126.2, 75.8, 54.9, 31.5, 20.2, 15.3.ppm. MS (ESI) m/z calculated for $C_{24}H_{22}N_2O_3$ $[M+H]^+$: 387.17; found $[M+H]^+$: 387.33

2-(1-(benzylimino)-2-hydroxy-3-methylbutyl)-1H-benzo[de]isoquinoline-1,3(2H)-dione (2c)



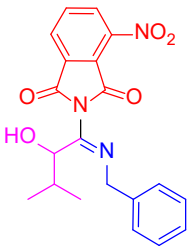
Synthesized according to procedure A from 1 mmol reaction as colorless liquid, yield: 40 mg (10 %); ^{1}H NMR (500 MHz, Chloroform-d) δ 8.64 (td, *J* = 7.4, 1.1 Hz, 2H), 8.30 (dt, *J* = 8.2, 1.2 Hz, 2H), 7.81 (ddd, *J* = 8.6, 7.4, 1.8 Hz, 2H), 7.37 – 7.18 (m, 5H), 4.59 (dd, *J* = 15.9, 1.5 Hz, 1H), 4.50 (dd, *J* = 15.9, 1.3 Hz, 1H), 4.47 – 4.42 (m, 1H), 2.10 – 1.98 (m, 1H), 1.10 (d, *J* = 6.9 Hz, 3H), 1.03 (d, *J* = 6.7 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 163.1, 162.4, 153.8, 138.2, 135.0, 132.0, 131.9, 131.8, 128.8, 128.4, 127.9, 127.2, 127.0, 122.0, 121.8, 77.3, 54.4, 30.9, 20.6, 15.2.ppm. MS (ESI) m/z calculated for $C_{24}H_{22}N_2O_3$ $[M+H]^+$: 387.17; found $[M+H]^+$: 387.33

2-(1-(benzylimino)-2-hydroxy-3-methylbutyl)-5-chloroisoindoline-1,3-dione (2d)



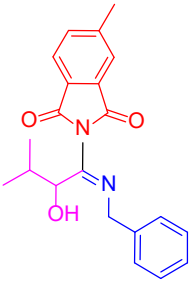
Synthesized according to procedure A from 1 mmol reaction as colorless liquid, yield: 242 mg (65 %); ^{1}H NMR (500 MHz, Chloroform-d) δ 7.97 – 7.81 (m, 2H), 7.74 (dd, *J* = 8.0, 1.8 Hz, 1H), 7.33 – 7.26 (m, 4H), 7.24 – 7.20 (m, 1H), 4.66 (dd, *J* = 16.1, 1.8 Hz, 1H), 4.62 – 4.54 (m, 1H), 4.48 (dd, *J* = 16.0, 1.3 Hz, 1H), 1.97 – 1.80 (m, 1H), 1.08 (d, *J* = 6.9 Hz, 3H), 0.88 (d, *J* = 6.8 Hz, 3H).ppm. MS (ESI) m/z calculated for $C_{20}H_{19}ClN_2O_3$ $[M+H]^+$: 371.12; found $[M+H]^+$: 371.28

2-(1-(benzylimino)-2-hydroxy-3-methylbutyl)-4-nitroisoindoline-1,3-dione (2e)



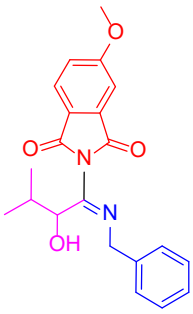
Synthesized according to procedure A from 1 mmol reaction as colorless liquid, yield: 271 mg (71 %); ^{1}H NMR (500 MHz, Chloroform-d) δ 8.25 – 8.14 (m, 2H), 8.01 (t, *J* = 7.9 Hz, 1H), 7.36 – 7.27 (m, 5H), 7.26 – 7.18 (m, 1H), 4.70 (d, *J* = 16.0 Hz, 1H), 4.59 – 4.49 (m, 2H), 2.02 – 1.90 (m, 1H), 1.10 (d, *J* = 6.9 Hz, 3H), 0.91 (d, *J* = 6.8 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 150.4, 145.4, 137.7, 136.6, 133.2, 129.6, 128.7, 128.6, 128.1, 127.7, 127.3, 123.0, 75.8, 54.9, 31.4, 20.1, 15.1.ppm. MS (ESI) m/z calculated for $C_{20}H_{19}N_3O_5$ $[M+H]^+$: 382.14; found $[M+H]^+$: 382.30

2-(1-(benzylimino)-2-hydroxy-3-methylbutyl)-5-methylisoindoline-1,3-dione (2f)



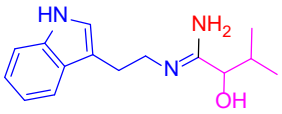
Synthesized according to procedure A from 1 mmol reaction as colorless liquid, yield: 220 mg (63 %); ^{1}H NMR (500 MHz, Chloroform-d) δ 7.83 (d, *J* = 7.7 Hz, 1H), 7.75 (s, 1H), 7.62 (dt, *J* = 7.7, 1.1 Hz, 1H), 7.37 – 7.30 (m, 4H), 7.30 – 7.22 (m, 1H), 4.71 (dd, *J* = 16.0, 1.8 Hz, 1H), 4.65 (dt, *J* = 3.1, 1.6 Hz, 1H), 4.53 (dd, *J* = 16.0, 1.3 Hz, 1H), 2.56 (s, 3H), 1.99 – 1.87 (m, 1H), 1.12 (d, *J* = 6.9 Hz, 3H), 0.92 (d, *J* = 6.8 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 151.8, 146.7, 138.3, 135.7, 131.8, 128.8, 128.5, 127.7, 127.1, 124.8, 124.2, 75.5, 54.8, 31.4, 22.1, 20.1, 15.1.ppm. MS (ESI) m/z calculated for $C_{21}H_{22}N_2O_3$ $[M+H]^+$: 351.17; found $[M+H]^+$: 351.34

2-(1-(benzylimino)-2-hydroxy-3-methylbutyl)-5-methoxyisoindoline-1,3-dione (2g)



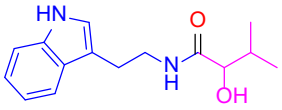
Synthesized according to procedure A from 1 mmol reaction as colorless liquid, yield: 280 mg (76 %); ^{1}H NMR (500 MHz, Chloroform-d) δ 7.81 (d, *J* = 8.4 Hz, 1H), 7.37 (d, *J* = 2.4 Hz, 1H), 7.34 – 7.27 (m, 4H), 7.26 – 7.18 (m, 2H), 4.67 (dd, *J* = 16.1, 1.8 Hz, 1H), 4.61 (dt, *J* = 3.0, 1.6 Hz, 1H), 4.50 (dd, *J* = 16.0, 1.3 Hz, 1H), 3.91 (s, 3H), 1.96 – 1.86 (m, 1H), 1.08 (d, *J* = 6.9 Hz, 3H), 0.89 (d, *J* = 6.8 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 165.4, 151.8, 138.3, 134.0, 128.7, 128.5, 127.7, 127.1, 126.1, 123.1, 121.1, 108.8, 75.5, 56.3, 54.8, 31.4, 20.1, 15.1.ppm. MS (ESI) m/z calculated for $C_{21}H_{22}N_2O_4$ $[M+H]^+$: 367.17; found $[M+H]^+$: 367.33

N'-(2-(1H-indol-3-yl)ethyl)-2-hydroxy-3-methylbutanimidamide (3a)



Synthesized according to procedure B from 1 mmol reaction as colorless liquid, yield: 109 mg (42 %);^{1}H NMR (500 MHz, Methanol-d_4) δ 7.59 (d, *J* = 7.9 Hz, 1H), 7.36 (d, *J* = 8.1 Hz, 1H), 7.16 (s, 1H), 7.13 (t, *J* = 7.6 Hz, 1H), 7.05 (t, *J* = 7.4 Hz, 1H), 4.12 (d, *J* = 3.9 Hz, 1H), 3.65 (t, *J* = 7.0 Hz, 2H), 3.12 (t, *J* = 7.1 Hz, 2H), 1.91 – 1.84 (m, 1H), 0.99 (d, *J* = 6.9 Hz, 3H), 0.78 (d, *J* = 6.8 Hz, 3H) ppm.

N-(2-(1H-indol-3-yl)ethyl)-2-hydroxy-3-methylbutanamide (4a)



Synthesized according to procedure C from 1 mmol reaction as colorless liquid, yield: 86 mg (33 %); ^{1}H NMR (500 MHz, Methanol-d_4) δ 7.65 (d, *J* = 7.9 Hz, 1H), 7.43 (d, *J* = 8.1 Hz, 1H), 7.23 (s, 1H), 7.21 – 7.16 (m, 1H), 7.11 (t, *J* = 7.5 Hz, 1H), 4.27 – 4.21 (m, 1H), 3.79 – 3.71 (m, 2H), 3.25 – 3.17 (m, 2H), 2.02 – 1.91 (m, 1H), 1.26 (t, *J* = 7.0 Hz, 1H), 1.05 (d, *J* = 6.8 Hz, 3H), 0.83 (d, *J* = 6.7 Hz, 3H). ^{13}C NMR (126 MHz, MeOD) δ 169.4, 136.9, 127.0, 122.7, 121.2, 118.5, 111.0, 110.1, 105.9, 42.3, 32.8, 23.4, 18.0, 14.1. ppm.