Nature-inspired remodeling of (aza)indoles to meta-aminoaryl nicotinates for late-stage conjugation of vitamin B₃ to (hetero)arylamines

Begur Vasanthkumar Varun, Kannan Vaithegi, Sihyeong Yi & Seung Bum Park

Despite the availability of numerous routes to substituted nicotinates based on the Bohlmann–Rahtz pyridine synthesis, the existing methods have several limitations, such as the inevitable ortho-substitutions and the inability to conjugate vitamin B₃ to other pharmaceutical agents. Inspired by the biosynthesis of nicotinic acid (a form of vitamin B₃) from tryptophan, we herein report the development of a strategy for the synthesis of meta-aminoaryl nicotinates from 3-formyl(aza)indoles. Our strategy is mechanistically different from the reported routes and involves the transformation of (aza)indole scaffolds into substituted meta-aminobiaryl scaffolds via Aldol-type addition and intramolecular cyclization followed by C–N bond cleavage and re-aromatization. Unlike previous synthetic routes, this biomimetic method utilizes propiolates as enamine precursors and thus allows access to ortho-unsubstituted nicotinates. In addition, the synthetic feasibility toward the halo-/boronic ester-substituted aminobiaryls clearly differentiates the present strategy from other cross-coupling strategies. Most importantly, our method enables the late-stage conjugation of bioactive (hetero)arylamines with nicotinates and nicotinamides and allows access to the previously unexplored chemical space for biomedical research.
Recent remarkable advancements in drug discovery have inspired the development of synthetic strategies aiming for the incorporation of bioactive skeletal features into newly synthesized molecules, as exemplified by late-stage functionalization, diversity-oriented synthesis (DOS), biology-oriented synthesis (BOS), and bioconjugation reactions. The key skeletal features of natural and synthetic bioactive compounds have been recognized as privileged structures with high biological relevance and the incorporation of such structures into molecular frameworks has been an important criterion for harnessing their biological activities. Therefore, the development of synthetic pathways for the incorporation of privileged structures into bioactive molecules, especially at the later stages of synthesis, may reveal bioactivities by expanding the chemical space toward unexplored biological applications via skeletal functionalization.

For example, Wang et al. recently demonstrated the enhanced pharmacological effects (synergistic effects) of the products obtained by the incorporation of the skeletal features of clopidogrel (antiplatelet drug) into SC-560 (COX-1 inhibitor) via transition-metal-based cyclodimerization, which showed that the conjugation of key skeletal features of drug moieties might induce synergistic effects. On the other hand, despite the existing limitations, much effort has been directed at the synthesis of antibody-drug conjugates through the covalent conjugation of small molecules to biomacromolecules. However, the late-stage covalent conjugation of therapeutic agents to other bioactive small molecules, such as vitamins, amino acids, and sugars, has not been well explored.

In-line with our continuous efforts to develop synthetic routes for privileged substructure-based DOS (pDOS) strategies and thereby increase molecular diversity, we aimed to establish a methodological concept for the late-stage modification of various small molecules with biologically-relevant substructures, such as vitamins. In particular, we focused on vitamin B3, also known as niacin or nicotinic acid, because of its simple structure and high biological relevance. Nicotinates and nicotinamide are pharmaceutical surrogates of nicotinic acid, and are used as dietary supplements to treat pellagra and other vitamin B3 deficiencies. Other classes of nicotinamide drugs include vasodilators, estrogen, androgen (Testosterone nicotinate), opioid analgesic and cough suppressants (Nicocodeine), anti-inflammatory agents (Mornillulinate), and hypolipidemic agents. On the other hand, (hetero)arylamines are key structural units that are found in numerous pharmaceuticals and feature a wide bioactivity range, as exemplified by their antipyretic, analgesic, anesthetic, antiviral, antibacterial, and anticancer activities. The Suzuki–Miyaura cross-coupling reaction is a standard protocol for constructing $C(s^2)p^2$–$C(s^2)$ bonds from halogenated arylamines and appropriate arylboronic acids, this reaction has yet to be successfully applied to simple and/or electron-deficient pyridine boronic acids, which includes nicotinate or nicotinamide scaffolds.

Because of the importance of the nicotinate moiety, numerous methods have been developed for its synthesis. Since the pioneering synthesis of 2-methylnicotinate by Dornow and Baumgarten in 1939 using β-alloxycarolein acetal and β-aminoconrotane, the Bohlmann–Rahtz synthesis, which employs substituted enamines and propargyl aldehydes/ketones, has been the major synthetic route to substituted pyridines, and its mechanistic principle has underpinned all further developments in the synthesis of nicotinates and other substituted pyridines, including the innovative Bagley modification of in situ α,β-substituted enamine generation (Fig. 1c).

In this sequence, there are also several MCR (multicomponent reaction) approaches developed for synthesis of polysubstituted pyridines sharing nicotinate/nicotinamide scaffold. However, the Bohlmann–Rahtz pyridine synthesis and its variants employ dicarbonyl compounds as enamine precursors and propargyl ketones or α,β-unsubstituted carbanols as the Michael acceptors, and therefore inevitably produce ortho-substituted nicotinates. To overcome this limitation, we carried out a careful analysis of the vitamin B3 biosynthetic process, which inspired us to design a strategy involving the conjugation of nicotinates with (hetero)arylamines from simple (aza)indoles (Fig. 1d). This unparalleled biosynthetic process involves an enzymatic C$_2$–C$_3$ bond cleavage of the tryptophan indole ring to produce N-formyl kynurenine, an important structural intermediate that can be subsequently transformed into a nicotinic acid, which is also a precursor to other forms of vitamin B3. To simulate the formation of N-formyl kynurenine containing the aniline moiety released from the indole unit of tryptophan in the vitamin B3 biosynthetic process, we hypothesized the skeletal remodeling of 3-formyl(aza)indole which allows the robust synthesis of meta-aminonicotinates with unfunctionalized C$_2$ and C$_3$ positions via alndal-type addition/dehydration and intramolecular cyclization followed by simultaneous re- aromatization and C–N bond cleavage (Fig. 1e and Supplementary Fig. 1).

Actually, highly regioselective direct C–H arylation at the C$_3$ position of substituted pyridines are possible (Fig. 1f) only when pyridines contain electron-withdrawing groups (–NO$_2$, –CN, –F, and –Cl) or directing group (carboximide). In addition, these methods cannot be employed to conjugate functional aromatics like arylamines to pyridines. Furthermore, a retrosynthetic analysis of the cross-coupling-based routes to ortho-nicotinated arylamines also revealed serious limitations, including long synthetic routes, limited substrate scope due to the poor accessibility of corresponding boronic esters, and apparent competitive side reactions (Fig. 1g). In fact, halogen (Br)– as well as boronic ester-substituted products, which could be valuable substrates for further diversification, proved impossible to access, thereby placing serious constraints on transition metal-based cross-coupling strategies. This proposed biomimetic strategy allowed the transformation of (aza)indole scaffolds to the meta- amino(hetero)aryl nicotinates in good yields and featured a broad substrate scope with limited side reactions while offering unique access to halogen/boronic ester-substituted (hetero)arylaminates conjugated to vitamin B3 along with robust conjugation of arylamines and nicotinate pharmaceuticals (Fig. 1h). This unique transformation involves the sequential reactions of different intermediates generated in the one-pot strategy and almost exclusively yields a single major product at the end of the final step. Although a number of research groups have attempted indole ring transformations to aminoaryl pyrazoles or other fused ring scaffolds, in this work, we show the robust biomimetic remodeling of (aza)indoles to the vitamin B3 scaffolds conjugated to (hetero)arylaminates as the last-stage transformation.

**Results**

**Reaction optimization and substrate scope.** We initially investigated our hypothesis (shown in Fig. 1e) for the remodeling of 3-formylindolones with the readily available β-aminoacrylate; however, the reaction did not proceed efficiently (<10% conversion, see Supplementary Figs. 1 and 3). Therefore, we postulated the in situ generation of β-aminoacrylate from the corresponding propiolates with NH$_4$OAc, which is known to form cationic complexes by activating the alkyne triple bond via cation–π interactions and also act as an ammonium source for the enamine synthesis (Supplementary Fig. 4). After a careful investigation with initial trials, we selected N-phenylsulfonyl-7-azaindole-3-carboxaldehyde (1a) and ethyl propiolate (2a) as...
**Fig. 1 Background for reaction development.**

- **a** Nicotinate pharmaceuticals
  - Active ingredient of cosmetics and rubefacients
  - Vasodilator
  - Nicotinate drugs
  - Estrogen medication
  - Estrapronic acid
  - Etofylline nicotinate

- **b** Aniline pharmaceuticals
  - Anesthetics
  - Benzocain
  - Butamben
  - Procaine
  - Antiarrhythmic
  - Paracetamol
  - Phenacetin
  - Procainamide

- **c** Previously reported synthesis of substituted nicotinates

- **d** Biosynthesis of nicotinates (Vitamin B3)
  - L-Tryptophan
  - Enzymatic C8 bond cleavage
  - Kynurenine
  - Multisteps
  - Nicotinic acid (Vitamin B3)

- **e** Reaction development inspired by Nature
  - Aldol-type reaction & dehydraton
  - Intramolecular cyclization
  - C-N bond cleavage
  - o-Nicotinated aniline

- **f** Selective C-H arylation of pyridine
  - C3-H selectivity
  - C4-H selectivity

- **g** Ortho-nicotination of arylamines; a plausible route
  - 3 Steps
  - Known

- **h** A new strategy inspired by Nature
  - (aza)indole scaffold
  - Advantages:
    - Limited side reactions
    - Broader substrate scope
    - Feasible with halo substitutions
    - Feasible with boronic acids
  - Boronic acid derivatives
  - Late stage skeletal transformation
  - Deuterated nicotinates
  - Conjugation of pharmaceuticals

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**Fig. 1 Background for reaction development.** a) Representative examples of commercially available bioactive nicotinates. b) Representative examples of aniline-based pharmaceuticals. c) Previously reported synthetic routes for substituted nicotinates with inevitable C2 and C6 substitutions. d) Biosynthetic process of vitamin B3 (a.k.a nicacin or nicotinic acid) from L-tryptophan. e) Reaction development with working hypothesis, which mimics the nature’s pathway for ortho-nicotinated anilines as the late-stage modification with vitamin B3 without substituents at the C2 and C6 positions. f) Regioselective direct C-H arylation of pyridines containing electron-withdrawing or directing groups. g) Plausible synthetic route for the conjugating anilinic compounds with vitamin B3 on the basis of the literature evidences. h) This study: synthetic strategy for conjugating anilinic compounds with vitamin B3 by mimicking nature’s biosynthetic pathway and its advantages.
the benchmark substrates for reaction optimization, wherein NH₄OAc was used as the ammonium source for in situ enamine generation. Following the investigation of various parameters (Supplementary Table 1), we determined the optimal reagent quantities to be 1.0 M 1a in EtOH containing 2a (1.2 equiv.) and NH₄OAc (4.0 equiv.). The reaction conditions involved heating the mixture at 100 °C, which yielded the desired product 3a (Fig. 2) in an average yield of 96%. Under the optimized conditions, we first explored the reactivity of the diversely N-substituted 7-azaindole-3-carboxaldehydes (1a–1m) containing sulfonamide, benzyl, aryl, and alkyl groups. Various N-substituted 7-azaindole-3-carboxaldehydes formed the desired meta-2-aminopyridyl nicotinates (3a–3m) in good to excellent yields, indicating that the electronic nature of the substituents at the azaindole N₁ position did not significantly affect the product yields or the ring transformation kinetics under the optimized conditions. However, N-acyl 7-azaindole-3-carboxaldehydes showed the significant decylation under the optimized condition (Supplementary Fig. 2).

After establishing the azaindole-based substrate scopes, we turned our attention to the indole derivatives. During the investigation of the substrate scope with N-sulfonylated indole derivatives as starting materials, we observed considerable byproduct formation, to address which, we performed additional solvent optimization (Supplementary Table 2). In the case of the N-sulfonylated indole derivatives, CH₃CN was identified as the best solvent for the reaction in the sealed vial at 100 °C, which delivered the products with minimal byproduct formation, despite ethanol being optimal for all other N-substituted (aza)indoles. With this condition, N-phenylsulfonyl, N-benzyl, and N-thiophen-2-ylmethyl indole-3-carboxaldehydes (1n–1p) were smoothly transformed into the desired products 3n, 3o, and 3p in yields of 90, 94, and 77%, respectively.

Unlike azaindoles, numerous substituted indoles are commercially available, thereby allowing for a broader substrate scope study. Therefore, the reaction compatibility with diverse electronic natures of the substituents on the indole rings was explored by placing methoxy, nitro, and bromo groups at various positions in the structure of 1n. Interestingly, all of the substrates (1q–1z) transformed to the corresponding desired products (3p–3z) in good to excellent yields irrespective of the electronic nature of the substituents, as well as the site of substitution. Notably, the formation of 3w required a longer reaction time (16 h) to reach the completion. However, the C₇ nitro- and bromo-substituted products were not obtained since the sulfonyl protection of the corresponding indole-3-carboxaldehydes was not successful. Furthermore, we expanded the reaction scope to the synthesis of meta-substituted nicotinamides 4a–4d in moderate to good yields by replacing ethyl propiolate with propiolamide as a reaction partner.

Use of (aza)indole-3-carboxaldehydes with a free –NH group. Encouraged by the versatility of the cascade ring transformation, we explored the possibility of ring cleavage of 3-formyl(aza) indoles bearing a free –NH group. To our delight, under the above optimized conditions, 6a and 6f were produced from 7-azaindole-3-carboxaldehyde (5a) and indole-3-carboxaldehyde...
carboxaldehyde (skeletons. Moreover, the easily accessible 4-chloro-7-azaindole-3-carboxaldehydes (5a, 5c-5e) provided significant diversity in the resulting heterobiaryl skeletons. Moreover, the easily accessible 4-chloro-7-azaindole-3-carboxaldehyde (5b) was employed to synthesize 6b which could be further diversified.

Indeed, the availability of a wide variety of indole derivatives allows the diversification of the corresponding meta-aminooaryl nicotinates in all possible substitution patterns around the indole scaffold. We then explored the substrate scope by extensively varying the substituents; methoxy (5g–5j), nitro (5k–5n), fluoro (5o–5r), bromo (5s–5v), and pinacol boronate (5w–5z) were evaluated at each of the C4–C7 positions of the indole-3-carboxaldehydes. Further, by considering the important roles of CF3 moiety in drug discovery, we also evaluated the substrate scope with CF3-substituted indole-3-carboxaldehydes (5w–5y).

As shown in Fig. 3, all substrates were transformed into the corresponding desired products (6g–6ac) in moderate to good yields. Similarly, under the optimized conditions, 5a and 5f readily reacted with propiolamide to afford 2-aminopyridyl (7a) and 2-aminophenyl nicotinamides (7b), respectively. It is worth mentioning that the synthesis of the bromo- and boronic ester-substituted products (3x–3z, 6s–6v, and 6z–6ac) makes our biomimetic strategy more attractive and showcases its versatility. These bromo- and boronic ester-derived products cannot be accessed by any other cross-coupling strategies, and are important substrates for further diversification at all possible positions around the aniline scaffold and thereby allow significantly enhanced exploration of the unexplored chemical space.

As shown in Figs. 2 and 3, we observed no considerable differences in the reactivity among substrates containing various substituents under the optimized conditions, which revealed that the reaction mechanism might feature more than one rate-limiting step in the sequential reaction pathway, and the overall reaction rate across the different steps may converge to a similar value irrespective of substrate substitution pattern. Therefore, a series of experiments were performed in parallel under identical reaction conditions featuring a short reaction time of 30 min to examine the initial rate of product formation, which may shed light on the influence of the electronic effects on the substrate reactivity. As shown in Supplementary Table 5, azaindole-3-carboxaldehyde (5a) was more reactive than the corresponding indole-3-carboxaldehyde (5f), and the nitro-substituted substrates (5i, 5m) were more reactive than the corresponding methoxy-substituted ones (5h, 5i). Therefore, the presence of electron-withdrawing groups on the indole ring increases their reactivity, possibly due to the increased rate of the C2–N bond cleavage.

**Synthetic application.** The developed nature-inspired synthetic strategy is based on the idea of conjugating bioactive small molecules with other privileged structures in the later stages of the synthesis, and this biomimetic route was used to establish a synthetic method for forging bioactive (hetero)arylamines conjugated with vitamin B3 (Fig. 4). For demonstration purposes, our biomimetic strategy was employed to construct a handful of covalently fused bioactive entities from the 3-formyl(aza)indole derivatives and

![Fig. 3 Substrate scopes for synthesis of nicotinated anilines/aminopyridines via (aza)indole skeleton remodeling. Reaction conditions: 5 (0.2 mmol), 2 (1.2 equiv.), NH4OAc (5.0 equiv.), and Zn(OTf)2 (10 mol%) at 120 °C. Reactions were performed in EIOH (2.0 mL) for 6 h in the case of azaindole-based substrates (6a–6e, 7a). Reactions were performed in CH3CN (2.0 mL) for 16 h in the case of indole-based substrates (6f–6ac, 7b). Yields of the isolated products (6 and 7) are reported.](https://www.nature.com/naturecommunications)
Fig. 4 Extending the scope of the reaction towards the synthesis of substituted bioactive niacinates and anilinic drugs. a Scope of the reaction for the synthesis of meta-substituted bioactive nicotinates. b Scope of the reaction for the synthesis of ortho-substituted bioactive N-protected or free arylamines. c A representative example of conjugates containing bioactive nicotinates and anilinic drugs via C-C bond. d, e Extension of the scope of our synthetic strategy for late-stage skeletal transformation of (aza)indole moiety in natural products and pharmaceuticals. See Supplementary Information for reaction condition and further details\(^{(a-g)}\).
the appropriate propiolates. Diverse pharmaceutically-active nicotinates were successfully linked to N-phenylsulfonyl-2-aminopyridines at its meta position. The N-phenylsulfonyl-protected 2-aminopyridine scaffold (red dot in Fig. 4a) was selected in preference to simple anilines or other aminopyridines, owing to its presence in many sulfa-based drugs, including sulfasalazine, which is designated as an essential medicine by the World Health Organization (WHO). Under the optimized conditions, 1a reacted with the appropriate propiolates (2a–2i) to afford products 3a and 3ab–3ae (75–96%), in which the meta position of the pharmaceutically-active nicotinates (ethyl, methyl, benzyl, n-hexyl, and myristyl nicotinates), known to be key ingredients in cosmetics and rubefacient creams, were covalently conjugated with N-phenylsulfonyl 2-aminopyridine scaffolds. In a similar fashion, we obtained 3af (96%) and 3ag (83%) in which the meta position of the vasodilating agents, such as etofylline nicotinate and cíclicronic, were conjugated with the N-phenylsulfonyl 2-aminopyridine scaffold. Furthermore, testosterone propionate and estradiol propionate reacted with 1a to afford 3ah (82%) and 3ai (67%), bearing scaffolds of testosterone nicotinate (an androgenic steroid) and estradiol nicotinate, respectively. 3ai was further proportioned to afford 3ai’ bearing the estrapronic acid (an estrogenic steroid) scaffold.

The presented biomimetic strategy also provides robust access to various amine Pharmaceuticals that are covalently fused with ethyl nicotinate (green dot in Fig. 4b). Under the optimized conditions, ethyl propionate was coupled with hydroxyl- and ethoxy-substituted indole-3-carboxaldehydes to afford 6af and 6ae, which were acetylated without further purification to furnish paracetamol 6ad’ (60%) and phenacetin 6ae’ (59%), in which the ethyl nicotinate is covalently conjugated at the ortho position. Similarly, N-acetalinidile-p-sulfonyl-7-azaindole-3-carboxaldehydes 1aj and 1ak were transformed to 3aj and nicotinated sulfanilamides 3ak, respectively, while nicotinated sulfapyridine 3aj’ was obtained by the deacylation of 3aj. Indole-3-carboxaldehydes substituted with various esters and amides at the C3 position afforded 6af, 6ag, and 6ah, which feature the key scaffolds of local anesthetics, namely benzocaine, butamben, and procain, respectively. As vasodilation can be associated with a local anesthetic response, the conjugation of vasodilators and local anesthetics is expected to result in a synergistic effect. The developed synthetic method was therefore employed for conjugating benzocaine to etofylline nicotinate and cíclicronic at the meta position to afford 6ai and 6aj, respectively (Fig. 4c). Further, to explore the feasibility of product diversification, we further transformed the nicotinamide scaffold in 3a, 3d, and 6a into vitamin B12 scaffold by hydrolysis, which afforded 3a’, 3d’, and 6a’ in good to excellent yields of 79, 76, and 91%, respectively.

Late-stage remodeling of (aza)indole core. Next, we attempted the late-stage skeletal transformation strategy to the indole-based natural products (Fig. 4d) and therapeutic agents (Fig. 4e). For example, naturally occurring dehydrohydrocorine 8a and therapeutic agents such as pindolol 11a (non-selective β-blocker) and OACI 14a (IPSC induction enhancer) were formulated to afford 9a, 12a, and 15a, respectively. These compounds successfully underwent a skeletal remodeling of the (aza)indoles under the standard reaction conditions. Interestingly, the expected product 10a from 9a was found to be susceptible to spontaneous oxidation at the benzylic position, and the analysis of the crude reaction mixture showed the formation of both 10a and its oxidized product 10a’ (72%). In the case of 11a, we obtained the inevitable N-formylated intermediate 12a’ via Vilsmeier-Haack reaction, and hydrolytic deformatylation allowed the conversion of 12a’ to 12a. Our skeletal transformation strategy allowed the formation of unique heterobiaryl product 13a (34%) via late-stage remodeling of 11a. Similarly, the formulated IPSC induction enhancer 15a underwent a ring transformation under the standard reaction conditions and afforded the heterobiaryl product 16a in good yield (67%).

Mechanistic studies. Based on our working hypothesis and literature precedence, we proposed different plausible reaction pathways (Fig. 5a) for the skeletal transformation of 3-formyl (aza)indoles to meta-aminoaryl nicotinates. To reveal the favorable mechanistic pathway, we designed a series of deuterium-labeling experiments (Fig. 5b). Based on our NMR analyses (1H, 13C, COSY, and HSQC) and literature reports, we assigned the 1H chemical shifts of the nicotinate scaffold. If the reaction proceeded by the unique heterobiaryl product 12a, which was found to be susceptible to spontaneous oxidation at the benzylic position, and the analysis of the crude reaction mixture showed the formation of both 10a and its oxidized product 10a’ (72%). In the case of 11a, we obtained the inevitable N-formylated intermediate 12a’ via Vilsmeier-Haack reaction, and hydrolytic deformatylation allowed the conversion of 12a’ to 12a. Our skeletal transformation strategy allowed the formation of unique heterobiaryl product 13a (34%) via late-stage remodeling of 11a. Similarly, the formulated IPSC induction enhancer 15a underwent a ring transformation under the standard reaction conditions and afforded the heterobiaryl product 16a in good yield (67%).
General procedure for the reaction of (aza)indole-3-carboxaldehydes. A 4-mL vial equipped with a magnetic stir bar and a Teflon-lined screwed cap was charged with 5 (0.2 mmol), 2 (1.2 equiv.), NH₄OAc (77.08 mg, 5 equiv.), and Zn(OTf)₂ (7.27 mg, 0.1 equiv.) in the appropriate solvent (2.0 mL, EtOH or CH₃CN). The vial was then sealed and heated at 120 °C for the desired times (6–16 h). Upon reaction completion checked by TLC analysis, the reaction mixture was concentrated under the reduced pressure, added with saturated aqueous NaHCO₃, and extracted with DCM (3 × 10 mL). The combined organic fractions were dried over anhydrous Na₂SO₄, filtered, and concentrated under reduced pressure. The crude compound was purified by silica-gel flash column chromatography to obtain the desired products bearing the nicotinate (6) or the nicotinamide (7) scaffolds.

Data availability
All data generated and analysed during this study are included in this article and its Supplementary Information, and also available from the authors upon reasonable request.

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Fig. 5 Plausible mechanisms of nature-inspired transformation of (aza)indole scaffolds into substituted meta-aminoaryl nicotinate scaffolds.

a Plausible mechanism A via imine formation and 6π electrocyclization followed by C–N bond cleavage and re-aromatization. Plausible mechanism B via Aldol-type addition, dehydration, and intramolecular cyclization followed by C–N bond cleavage and re-aromatization. Each proton in meta-aminoaryl nicotinates was color-coded to track its sources in starting materials. b Deuterium-labeling experiments revealed that our structural remodeling of (aza) indoles into substituted meta-aminoaryl nicotinate scaffolds occurs via plausible pathway B, as confirmed by NMR experiments.

Fig. 5 Plausible mechanisms of nature-inspired transformation of (aza)indole scaffolds into substituted meta-aminoaryl nicotinate scaffolds.

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Additional information
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Correspondence and requests for materials should be addressed to S.B.P.
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