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Synthesis of naphtholactams and their biological evaluation against *Pseudomonas aeruginosa*

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Dedicated to Prof. Samir Zard and his contribution to radical chemistry

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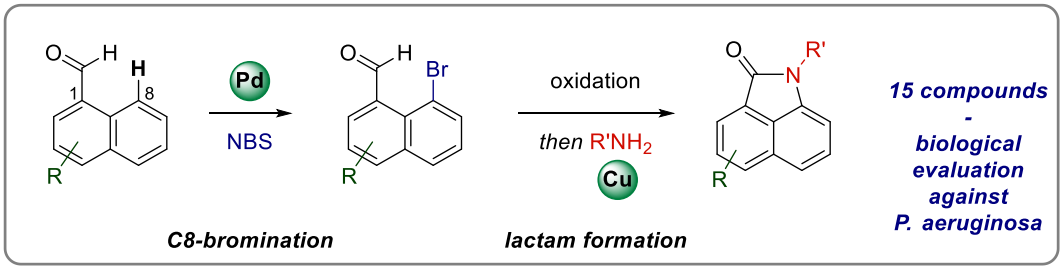
Abstract

The naphtholactam scaffold can be found in a lot of natural products or bioactive compounds, with some previous reports highlighting its antibacterial properties. In this context, we report the synthesis of a library of naphtholactams bearing various functional groups and their biological evaluation against the bacterium *Pseudomonas aeruginosa*. Their synthesis was accomplished through a concise three-step process, from readily available naphthaldehydes, involving a palladium-catalyzed C8-bromination followed by an oxidation/lactam formation sequence.



Keywords: Naphtholactam, C–H activation, catalysis, *Pseudomonas aeruginosa*

Introduction

Naphtholactam, or benzo[*cd*]indol-2(1*H*)-one, constitutes a significant skeleton frequently encountered in biologically active compounds (Figure 1). Notably, naphtholactams containing a sulfonamide group have demonstrated their utility as inhibitors of tumor necrosis factor-α, exemplified by EJMC-1,[1] as well as BET bromodomain inhibitors.[2] This structural motif also finds prevalence in various natural products, such as aspergilline F,[3] cyclopiamide A,[4] and the extensive family of aristolactams.[5,6] In 2019, Zhao and Xue's group evaluated a small library of naphtholactams and could unveiled some inhibition properties against *Pseudomonas aeruginosa*.[7] Given the detrimental impact of this bacterium and the escalating challenge of drug resistance, coupled with our profound interest in this topic,[8] we were keen to develop a fast access to a library of naphtholactams and to evaluate their activity against *P. aeruginosa*.

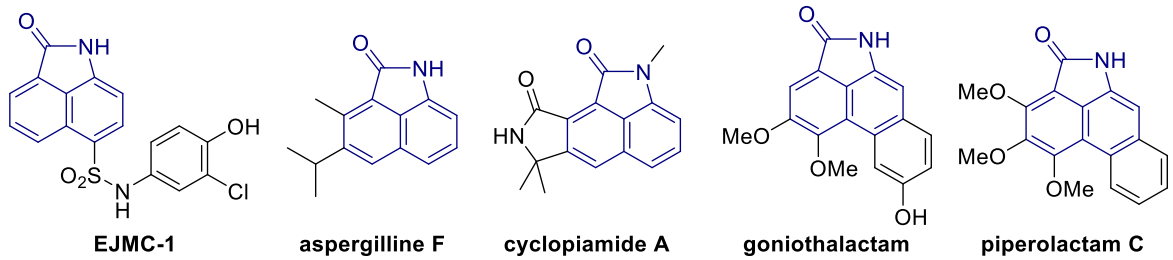
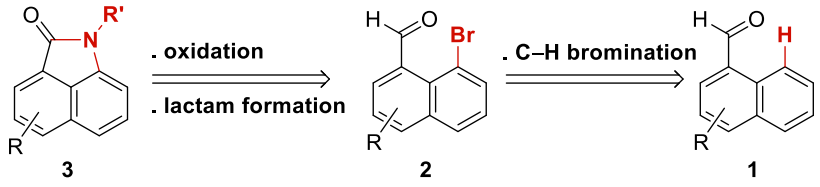


Figure 1. Natural products bearing a naphtholactam core.

Due to the widespread interest they have garnered, numerous synthetic routes for naphtholactams have been reported in the literature.[9,10,11] On our part, our approach involves the application of our prior research concerning 1-carbonylnaphthalene C–H activation.[12,13,14] This strategy aims to attain desired skeleton **3** through a two-step process from 1-naphthaldehydes **1**. First, the lactam moiety could be formed *via* the oxidation of 8-bromo-1-naphthaldehydes **2**, followed by a coupling reaction involving an external amine. Subsequently, these bromo intermediates **2** could be synthesized by a C8-bromination of easily accessible 1-naphthaldehydes **1** (Scheme 1).

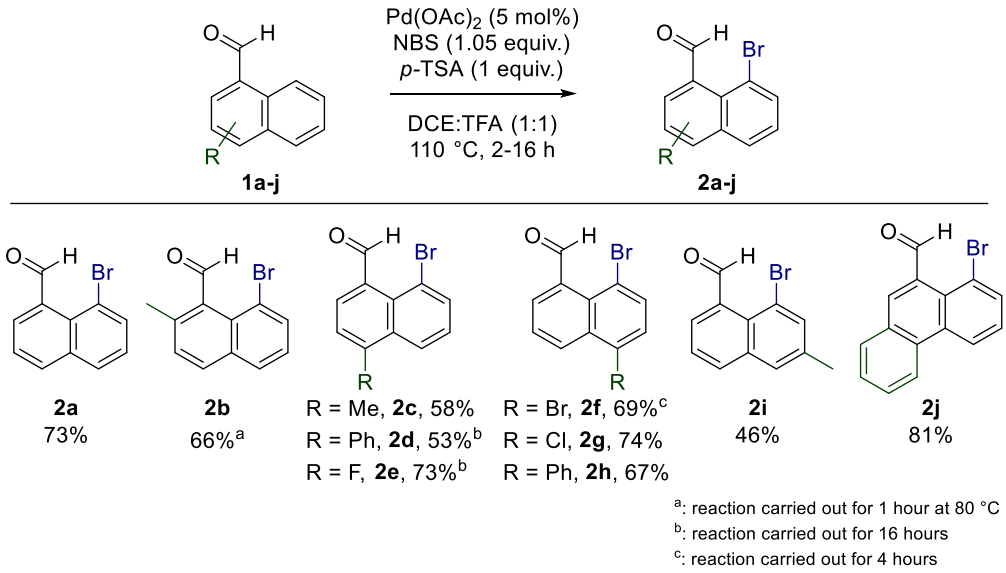


Scheme 1. Retrosynthesis of naphtholactam skeleton thanks to a C–H activation step.

Herein, we report the synthesis of 15 naphtholactams bearing several different functional groups and their evaluation as inhibitor of the bacterium *P. aeruginosa*.

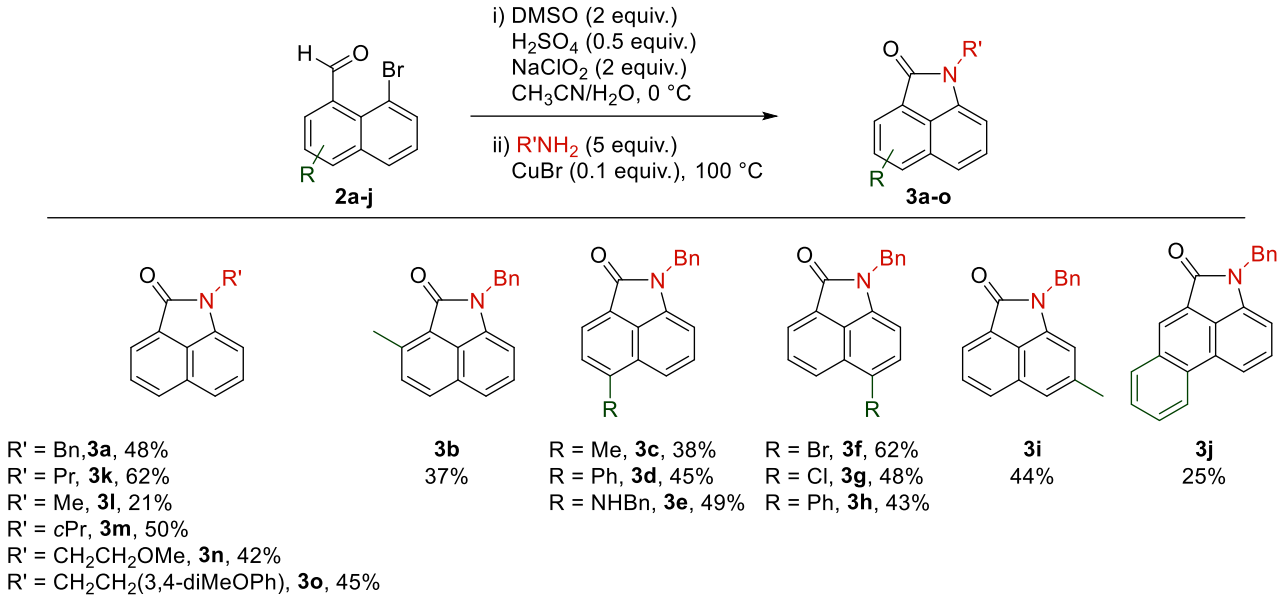
Results and Discussion

First, our previous C8-bromination methodology was applied to several 1-naphthaldehydes **1a-j** and C8-brominated naphthalenes **2a-j** were isolated in moderate to good yields (Scheme 2).[14] This C–H bromination reaction was effectively accomplished by employing palladium diacetate as catalyst and *N*-bromosuccinimide as bromination agent under acidic conditions. While the conventional procedure involved a 2-hour reaction at 110 °C, adjustments were made to the reaction time and temperature taking into consideration the reactivity of 1-naphthaldehydes.



Scheme 2. C8-bromination of 1-naphthaldehydes.

With a set of 8-bromo-1-naphthaldehydes **2a-j** at our disposal, a two-step process was employed to construct the lactam ring. In the initial step, the aldehyde moiety underwent oxidation into carboxylic acid through the utilization of sodium chlorite and DMSO. Then, the resultant crude carboxylic acid was subjected in a copper-catalyzed coupling reaction in presence of a primary amine used as solvent, leading to naphtholactams **3a-o** (Scheme 3). First, benzylamine was used as primary amine in this reaction and benzylprotected-naphtholactams **3a-j** were obtained in acceptable yields (25-62% over the two steps). The choice of such compounds, bearing *N*-benzyl group, had been retained for further investigation due to previous observations.[6] They were incorporating various substituents such as methyl, phenyl or halogen atom at position 2, 4, 5 and 6. Interestingly, the reaction involving 8-bromo-4-fluoro-1-naphthaldehyde **2e** was accompanied by an aromatic nucleophilic substitution, leading to the isolation of naphtholactam **3e** bearing a benzylamine moiety in position 4 in 49% yield. Despite reducing the amount of benzylamine used in the second step, there was still no observation of fluorinated naphtholactam formation. Finally, tetracyclic lactam **3j** was synthesized in a moderate 25% yield. Additional chemo-diversity was attained starting from naphthaldehyde **2a** which, after oxidation to the corresponding carboxylic acid, was treated with various primary amines to synthesize five benzo[*cd*]indol-2(1H)-one **3k-o**. Notably, in the synthesis of methyl-protected naphtholactam **3l**, the amide formation reaction was carried out with methylamine hydrochloride and triethylamine.



Scheme 3. Synthesis of naphtholactams.

After synthesizing these naphtholactams with various substitutions, we assessed their biological activity against *P. aeruginosa*. Naphtholactams **3** were solubilized in DMSO, and we initially determined the highest DMSO concentration tolerated by the *P. aeruginosa* PAO1 strain. A 3% DMSO concentration appeared to be completely tolerated by the bacteria. Zhao and Xue's group found that 1% was the maximum concentration that did not affect the growth of their strain but this discrepancy could be easily attributed to the phenotypic variations that exist between the different PAO1 strains among laboratories.[15]

The naphtholactams, once dissolved in DMSO, promptly form precipitates upon dilution in LB media, even at low concentrations. However, when a 2% concentration of the commonly employed non-ionic emulsifier Tween 80 was added into the culture media, the solubility of naphtholactams was achieved without any deleterious effects on bacterial growth. The MIC of the naphtholactams were then determined by microdilution method in accordance with the guidelines of the Clinical and Laboratory Standards Institute with the exception of growth medium since LB medium with 2% Tween 80 was used. No MIC could be determined, as none of naphtholactams at 300 µg/ml or below completely inhibited bacterial growth in these conditions. However, among the various naphtholactams tested, compounds **3a**, **3b**, **3c**, **3d** and **3h** at a 300 µg/mL concentration exhibited a minor reduction in bacterial growth, as indicated by the growth curves illustrated in figure 2. This result confirms that some naphtholactams possess inherent antibacterial properties against *P. aeruginosa* but the low solubilization of these compounds appeared to be an obstacle to their biological use. This aspect was not developed in Zhao and Xue's study and may explain the differences in the biological activities observed in our respective works.

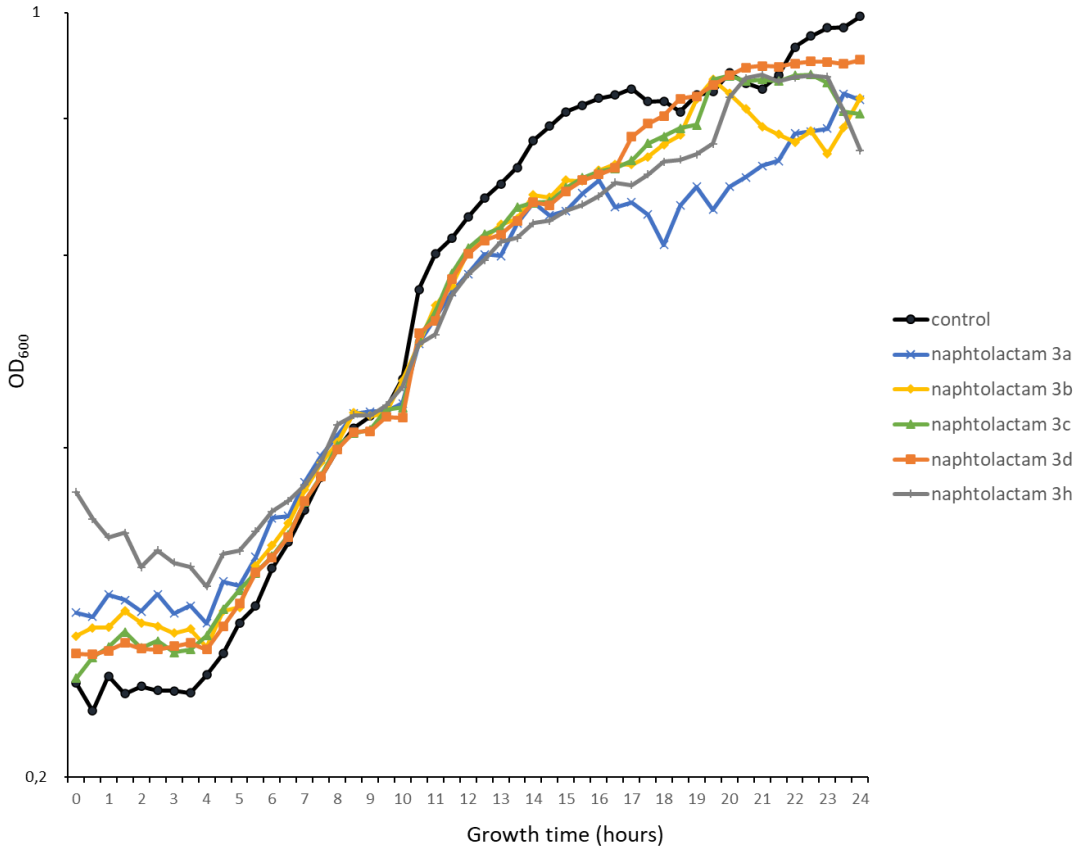


Figure 2. *P. aerugonisa* PAO1 growth inhibition by naphtholactams.

Conclusions

In summary, we have detailed the concise synthesis of a library of 15 naphtholactams. Comprehensive evaluation of the antibacterial efficacy of these compounds against *P. aeruginosa* has been conducted, revealing modest inhibitory activity in some cases. Unfortunately, it is regrettable that the investigation has been somewhat impeded by solubility challenges, which have hindered the pursuit of more extensive analyses.

Experimental Section

General. All commercial materials were purchased from Alfa Aesar, Sigma-Aldrich, TCI, Fluorochem or BLDpharm and used without further purification. Reactions were monitored by TLC on Merck silica gel 60-F254 aluminium sheets (ref.1.05554.0001), using UV absorption basic permanganate (1% $KMnO_4$ + 15% Na_2CO_3 in water) as staining system. Column chromatography was carried out on silica gel (40-63 µm). Petroleum ether refers to 40/60 petroleum ether. NMR spectra were recorded on a Bruker 400 MHz Avance III spectrometer. Proton chemical shifts are reported in ppm (δ) with the solvent resonance employed as the internal standard ($CDCl_3$ δ 7.26). Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, q = quintuplet, h = heptuplet, m = multiplet, br = broad), coupling constants (Hz) and integration.

Carbon chemical shifts are reported in ppm with the solvent resonance as the internal standard ($CDCl_3$ δ 77.16). IR spectra were performed on a Perkin-Elmer FT 1600 spectrometer with wavelengths in cm^{-1} and only peaks of interest are reported. HighResolution Mass Spectra (HRMS) were carried out with a time-TOF mass spectrometer (Bruker). Electrospray source has been used in positive mode. Melting points (Mp) were determined on a Stuart SMP3 apparatus and were left uncorrected.

General procedure A: C8-bromination of 1-naphthaldehydes

In a tube, naphthaldehyde derivative **1** (1 equiv.), NBS (1.05 equiv), $Pd(OAc)_2$ (5 mol %) and *p*TSA (1 equiv.) were dissolved in a mixture of DCE:TFA (1:1, 0.5 M). The tube was sealed and the reaction was stirred at 110 °C for 2-16 h and monitored by ^{1}H NMR. After completion, the reaction was cooled to room temperature, dissolved with DCM and quenched with a saturated aqueous solution of $NaHCO_3$. Extraction was performed three times with DCM. Organic phases were gathered, dried over $MgSO_4$, filtered and then concentrated *in vacuo*. The residue was purified by flash chromatography on silica gel.

8-Bromo-1-naphthaldehydes **2a-j** were previously described.[14]

General procedure B: lactam synthesis

In a flask, 8-bromo-1-naphthaldehyde **2** (1 equiv.) and dimethyl sulfoxide (2 equiv.) were dissolved in acetonitrile (0.2 M) and water (6 M) at 0 °C. Then, sulfuric acid (0.5 equiv.) was introduced dropwise. A solution of sodium chlorite (2 equiv.) in water (1 M) was added dropwise in the mixture. Then, the mixture was stirred at 0 °C for 2 h. The reaction was quenched by water and the aqueous phase was extracted with EtOAc. The organic phases were gathered, washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo* to afford corresponding carboxylic acid.

In a vial, the carboxylic acid (1 equiv.), copper (+I) bromide (10 mol %) and an amine (5 equiv.) were stirred at 100 °C for 16 h. The mixture was quenched by HCl_{aq} (3 M). Then, the aqueous phase was extracted with EtOAc, the organic phases were gathered, washed by brine, dried over $MgSO_4$, filtered and concentrated in vacuo. The crude compound was purified by column chromatography over silica gel to provide the naphtholactam **3**.

1-benzylbenzo[*cd*]indol-2(1*H*)-one (3a). Prepared according to general procedure B from 0.5 mmol of 8-bromo-1-naphthaldehyde **2a** and benzylamine. The crude compound was purified by column chromatography over silica gel (petroleum ether/Et_2O = 4:1) to provide **3a** as an orange solid (62 mg, 48% yield). Spectroscopic data are in agreement with the published data. R_f = 0.31 (petroleum ether/ Et_2O = 4:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.11 (dd, *J* = 7.0, 0.6 Hz, 1H), 8.00 (dd, *J* = 8.1, 0.6 Hz, 1H), 7.72 (dd, *J* = 8.1, 7.0 Hz, 1H), 7.50 (dd, *J* = 8.5, 0.5 Hz, 1H), 7.39 – 7.23 (m, 6H), 6.78 (dd, *J* = 7.1, 0.5 Hz, 1H), 5.13 (s, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.2, 139.2, 136.9, 131.0, 129.2, 128.8 (2C), 128.8, 128.6, 127.7, 127.6 (2C), 126.5, 125.4, 124.6, 120.4, 105.9, 44.1.

Spectroscopic data are in agreement with literature.[7]

1-Benzyl-3-methylbenzo[*cd*]indol-2(1*H*)-one (3b): Prepared according to general procedure B from 0.26 mmol of 8-bromo-2-methyl-1-naphthaldehyde **2b** and benzylamine. In this case, sodium chlorite (2 equiv) was added after 2 hours of reaction and mixture was stirred over night at r.t. to allow total conversion into the acid. The crude compound was purified by column chromatography over silica gel (petroleum ether/EtOAc = 4:1) to provide **3b** as a white solid (26 mg, 37%). Mp = 99°C; R_f = 0.5 (petroleum ether/EtOAc = 4:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.89 (d, *J* = 8.4 Hz, 1H), 7.48 (td, *J* = 8.4, 0.6 Hz, 2H), 7.42 – 7.22 (m, 6H), 6.78 (dd, *J* = 7.1, 0.5 Hz, 1H), 5.13 (s, 2H), 2.89 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.5, 139.6, 138.3, 137.1, 131.9, 130.6, 128.7 (2C), 127.6 (2C), 127.5, 127.4, 127.4, 125.2, 122.9, 120.1, 105.6, 43.8, 17.7; **IR** ν (neat) 2987, 1695, 1482, 1250, 1066 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{19}H_{15}NO$ 274,1226, found 274,1225.

1-Benzyl-5-methylbenzo[*cd*]indol-2(1*H*)-one (3c): Prepared according to general procedure B from 0.24 mmol of 8-bromo-4-methyl-1-naphthaldehyde **2c** and benzylamine. The crude compound was purified by column chromatography over silica gel (petroleum ether/EtOAc = 4:1) to provide **3c** as a yellow solid (25 mg, 38%). Mp = 92°C; R_f = 0.52 (petroleum ether/EtOAc = 4:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.00 (d, *J* = 7.1 Hz, 1H), 7.58 (dd, *J* = 8.6, 0.5 Hz, 1H), 7.52 (dd, *J* = 7.1, 0.9 Hz, 1H), 7.41 – 7.21 (m, 6H), 6.76 (dd, *J* = 7.1, 0.5 Hz, 1H), 5.12 (s, 2H), 2.76 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.2, 141.1, 139.5, 137.1, 129.2, 128.9, 128.8 (2C), 128.2, 127.6 (2C), 127.6, 125.6, 124.8, 124.5, 117.8, 105.8, 44.0, 18.7; IR ν (neat) 2924, 1698, 1497, 1307, 766 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{19}H_{15}NO$ 274,1225, found 274,1226.

1-Benzyl-5-phenylbenzo[*cd*]indol-2(1*H*)-one (3d): Prepared according to general procedure B from 0.23 mmol of 8-bromo-4-phenyl-1-naphthaldehyde **2d** and benzylamine. The crude compound was purified by column chromatography over silica gel (petroleum ether/EtOAc = 4:1) to provide **3d** as a brown solid (35 mg, 45%). Mp = 152°C; R_f = 0.6 (petroleum ether/EtOAc = 4:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.18 (d, *J* = 7.2 Hz, 1H), 7.72 (d, *J* = 7.2 Hz, 1H), 7.63 – 7.44 (m, 6H), 7.42 – 7.22 (m, 6H), 6.81 (dd, *J* = 7.1, 0.5 Hz, 1H), 5.17 (s, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.0, 144.9, 139.3, 138.9, 136.9, 130.0 (2C), 129.5, 128.8 (2C), 128.7 (2C), 128.6, 128.2, 127.7, 127.6 (2C), 127.5, 125.9, 125.5, 124.6, 119.5, 105.9, 44.1; IR ν (neat) 2922, 1702, 1620, 1490, 1393 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{24}H_{17}NO$ 336,1383, found 336,1378.

1-Benzyl-5-(benzylamino)benzo[*cd*]indol-2(1*H*)-one (3e): Prepared according to general procedure B from 0.24 mmol of 8-bromo-4-fluoro-1-naphthaldehyde **2e** and benzylamine. The crude compound was purified by column chromatography over silica gel (petroleum ether/EtOAc = 1:1) to provide **3e** as a brown solid (35 mg, 45%). Mp = 219°C; R_f = 0.52 (petroleum ether/EtOAc = 1:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.98 (d, *J* = 7.9 Hz, 1H), 7.43 – 7.26 (m, 14H), 6.74 (d, *J* = 7.1 Hz, 1H), 6.96 (d, *J* = 7.9 Hz, 1H), 5.49 (br s, 1H), 5.13 (s, 2H), 4.61 (d, *J* = 5.2 Hz, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.1, 148.7, 139.1, 137.7, 137.5, 129.1 (2C), 128.8 (2C), 128.0, 127.9, 127.7 (2C), 127.5 (2C), 127.4, 126.8, 126.4, 118.2, 113.9, 113.3, 106.4, 105.9, 48.1, 43.9; IR ν (neat) 3357, 1670, 1494, 1294, 1241 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{25}H_{20}N_2O$ 365,1648, found 365,1642.

1-benzyl-6-bromobenzo[*cd*]indol-2(1H)-one (3f): Prepared according to general procedure B from 0.11 mmol of 8-bromo-5-bromo-1-naphthaldehyde **2f** and benzylamine. The crude compound was purified by column chromatography over silica gel (petroleum ether/EtOAc = 9:1) to provide **3f** (23 mg, 62%). R_f = 0.28 (petroleum ether/EtOAc = 9:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.15 (dd, *J* =7.7, 3.5 Hz, 2H), 7.82 (dd, *J* = 8.2, 7.2 Hz, 1H), 7.56 (d, *J* = 7.5 Hz, 1H), 7.38 – 7.26 (m, 5H), 6.61 (d, *J* = 7.6 Hz, 1H), 5.11 (s, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 167.6, 138.9, 136.5, 131.3, 130.6, 129.9, 129.1, 129.0 (2C), 127.86, 127.6 (2C), 126.8, 126.4, 125.5, 114.3, 107.0, 44.1; IR ν (neat) 3027, 1705, 1630, 1492, 1377 cm^{-1}; HRMS (ESI) *m/z* [M+H]+ calcd for $C_{18}H_{13}BrNO$ 338.0175, found 338.0178.

1-benzyl-6-chlorobenzo[*cd*]indol-2(1H)-one (3g): Prepared according to general procedure B from 0.085 mmol of 8-bromo-5-chloro-1-naphthaldehyde **2g** and benzylamine. The crude compound was purified by column chromatography over silica gel (petroleum ether/EtOAc = 9:1) to provide **3g** (12 mg, 48%). R_f = 0.32 (petroleum ether/EtOAc = 9:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.23 (d, *J* = 8.3 Hz, 1H), 8.16 (d, *J* = 7.1 Hz, 1H), 7.82 (dd, *J* = 8.3, 7.0 Hz, 1H), 7.40 – 7.24 (m, 6H), 6.66 (d, *J* = 7.6 Hz, 1H), 5.11 (s, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 167.8, 138.2, 136.6, 129.7, 129.0 (2C), 128.5, 127.9, 127.9, 127.7, 127.6 (2C), 126.8, 126.3, 125.5, 125.2, 106.4, 44.2; IR ν (neat) 3029, 1706, 1632, 1468, 1380 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{18}H_{13}ClNO$ 294.0680, found 294.0678.

1-benzyl-6-phenylbenzo[*cd*]indol-2(1H)-one (3h): Prepared according to general procedure B from 0.16 mmol of 8-bromo-5-phenyl-1-naphthaldehyde **2h** and benzylamine. The crude compound was purified by column chromatography over silica gel (petroleum ether/EtOAc = 9:1) to provide **3h** (23 mg, 43%). R_f = 0.30 (petroleum ether/EtOAc = 9:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.19 – 8.12 (m, 2H), 7.73 (dd, *J* = 8.3, 7.0 Hz, 1H),

7.52 – 7.49 (m, 3H), 7.44 – 7.39 (m, 3H), 7.38 – 7.31 (m, 4H), 7.30 – 7.27 (m, 1H), 6.86 (d, *J* = 7.3 Hz, 1H), 5.18 (s, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.2, 139.2, 138.6, 137.0, 134.5, 130.3, 129.9 (2C), 129.0, 128.9 (2C), 128.7, 128.7 (2C), 127.9, 127.7 (2C), 127.7, 127.5, 126.8, 125.7, 124.7, 106.1, 44.1; IR ν (neat) 2972, 1697, 1627, 1599 1306 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{24}H_{18}NO$ 336.1383, found 336.1377.

1-benzyl-7-methylbenzo[*cd*]indol-2(1H)-one (3i): Prepared according to general procedure B from 0.10 mmol of 8-bromo-6-methyl-1-naphthaldehyde **2i** and benzylamine. The crude compound was purified by column chromatography over silica gel (petroleum ether/EtOAc = 9:1) to provide **3i** (12 mg, 44%). R_f = 0.30 (petroleum ether/EtOAc = 9:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.04 (d, *J* = 7.0 Hz, 1H), 7.92 (d, *J* = 8.0 Hz, 1H), 7.69 (dd, *J* = 8.0, 7.0 Hz, 1H), 7.38-7.29 (m, 6H), 6.63 (s, 1H), 5.12 (s, 2H), 2.47 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 166.4, 139.0, 137.1, 136.0, 139.3, 133.1, 129.4, 128.9, 128.87 (2C), 127.6, 127.5 (2C), 126.9, 123.6, 119.1, 108.2, 44.0, 23.2; IR ν (neat) 2972, 1701, 1637, 1305, 1101 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{19}H_{16}NO$ 274,1226, found 274,1228.

4-Benzylnaphtho[3,2,1-*cd*]indol-5(4*H*)-one one (3j): Prepared according to general procedure B from 0.35 mmol of 8-bromophenanthrene-9-carbaldehyde **2j** and benzylamine. The crude compound was purified by column chromatography over silica gel (petroleum ether/EtOAc = 4:1) to provide **3j** as a brown solid (27 mg, 25%). Mp = 158°C; R_f = 0.44 (petroleum ether/EtOAc = 4:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.64 (d, *J* = 8.3 Hz, 1H), 8.51 (s, 1H), 8.18 (d, *J* = 8.1 Hz, 1H), 8.11 (d, *J* = 8.4 Hz, 1H), 7.86 – 7.78 (m, 1H), 7.71 (t, *J* = 7.5 Hz, 1H), 7.54 (dd, *J* = 8.4, 7.3 Hz, 1H), 7.40 (d, *J* = 7.4 Hz, 2H), 7.35 – 7.27 (m, 3H), 6.90 (d, *J* = 7.3 Hz, 1H), 5.18 (s, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.9, 139.5, 136.8, 133.5, 132.2, 132.0, 129.3, 128.9, 128.9 (2C), 127.7, 127.66 (2C), 127.5, 127.2, 126.8, 124.9, 123.6, 121.8, 116.2, 106.3, 44.2.; IR ν (neat) 2971, 1702, 1492, 1213, 1075 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{22}H_{16}NO$ 310,1226, found310,1222.

1-Propylbenzo[*cd*]indol-2(1*H*)-one (3k). Prepared according to general procedure B from 0.1 mmol of 8-bromo-1-naphthaldehyde **2a** and propylamine. The crude compound was purified by column chromatography over silica gel (petroleum ether/DCM = 4:1) to provide **3k** as a white solid (13 mg, 62%). Spectroscopic data are in agreement with the published data. R_f = 0.44 (petroleum ether/DCM = 4:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.06 (dd, *J* = 7.0, 0.6 Hz, 1H), 8.00 (dd, *J* = 8.1, 0.7 Hz, 1H), 7.70 (dd, *J* = 8.1, 7.0 Hz, 1H), 7.52 (dd, *J* = 8.5, 0.6 Hz, 1H), 7.45 (dd, *J* = 8.5, 6.9 Hz, 1H), 6.91 (dd, *J* = 7.0, 0.6 Hz, 1H), 3.89 (t, *J* = 7.2 Hz, 2H), 1.82 (h, *J* = 7.5 Hz, 2H), 1.00 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.3, 139.8, 130.8, 129.2, 128.8, 128.6, 126.9, 125.3, 124.3, 120.3, 105.1, 42.0, 22.2, 11.6.

Spectroscopic data are in agreement with literature.[7]

1-methylbenzo[*cd*]indol-2(1H)-one (3l): Prepared according to general procedure B from 0.21 mmol of 8-bromo-1-naphthaldehyde **2a** and methylamine hydrochloride (5 equiv.) and triethylamine (5 equiv.). The crude compound was purified by column chromatography over silica gel (petroleum ether/EtOAc = 7:3) to provide **3l** (8 mg, 21%). R_f = 0.54 (petroleum ether/EtOAc = 7:3); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.07 (d, *J* = 7.0 Hz, 1H), 8.01 (dd, *J* = 8.1, 0.5 Hz, 1H), 7.71 (dd, *J* = 8.1, 7.0 Hz, 1H), 7.54 (dd, *J* = 8.5, 0.5 Hz, 1H), 7.48 (dd, *J* = 8.5, 6.9 Hz, 1H), 6.91 (dd, J = 6.9, 0.5 Hz, 1H), 3.46 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 168.4, 140.2, 130.9, 129.1, 128.8, 128.6, 126.9, 125.3, 124.4, 120.5, 104.9, 26.5.

Spectroscopic data are in agreement with literature.[16]

1-cyclopropylbenzo[*cd*]indol-2(1H)-one (3m): Prepared according to general procedure B from 0.21 mmol of 8-bromo-1-naphthaldehyde **2a** and cyclopropylamine. The crude compound was purified by column chromatography over silica gel (petroleum ether/EtOAc = 8:2) to provide **3m** (22 mg, 50%). R_f = 0.50 (petroleum ether/EtOAc = 8:2); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.04-7.99 (m, 2H), 7.69 (dd, *J* = 8.1, 7.0 Hz, 1H), 7.53 (dd, *J* = 8.5, 0.6 Hz, 1H), 7.47 (dd, *J* = 8.5, 6.9 Hz, 1H), 7.11 (dd, *J* = 6.9, 0.6 Hz, 1H), 2.92 (dq, J = 6.8, 3.8 Hz, 1H), 1.16 – 1.11 (m, 2H), 1.07 – 1.00 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 169.1, 140.4, 130.9, 129.2, 128.8,

128.7, 126.7, 125.1, 124.2, 120.3, 105.9, 22.3, 6.1 (2C).; IR ν (neat) 3027, 1704, 1633, 1400, 1105 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{14}H_{12}NO$ 210.0913, found 210.0917.

1-(2-methoxyethyl) benzo[*cd*]indol-2(1H)-one (3n): Prepared according to general procedure B from 0.21 mmol of 8-bromo-1-naphthaldehyde **2a** and 2-methoxyethylamine. The crude compound was purified by column chromatography over silica gel (petroleum ether/EtOAc = 3:1) to provide **3n** (20 mg, 42%). R_f = 0.33 (petroleum ether/EtOAc = 9:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.07 (d, *J* = 7.0 Hz, 1H), 8.02 (d, *J* = 8.1 Hz, 1H), 7.71 (dd, *J* = 8.1, 7.0 Hz, 1H), 7.58 – 7.44 (m, 2H), 7.03 (d, *J* = 7.0 Hz, 1H), 4.12 (t, *J* = 5.6 Hz, 2H), 3.72 (t, *J* = 5.6 Hz, 2H), 3.35 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 168.3, 139.9, 131.0, 129.2, 128.7, 128.7, 126.7, 125.3, 124.4, 120.4, 105.9, 71.1, 59.1, 40.6; IR ν (neat) 2987, 1698, 1633, 1495, 1116 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{14}H_{14}NO_2$ 228.1019, found 228.1024.

1-(3,4-Dimethoxyphenethyl)benzo[*cd*]indol-2(1*H*)-one (3o): Prepared according to general procedure B from 0.36 mmol of 8-bromo-1-naphthaldehyde **2a** and 3,4-dimethoxyphenethylamine. The crude compound was purified by column chromatography over silica gel (petroleum ether/DCM = 1:1) to provide **3o** as a brown solid (54 mg, 45%). Mp = 94°C; R_f = 0.2 (petroleum ether/EtOAc = 1:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.05 (dd, *J* = 7.0, 0.6 Hz, 1H), 7.99 (dd, *J* = 8.2, 0.6 Hz, 1H), 7.69 (dd, *J* = 8.1, 7.0 Hz, 1H), 7.49 (dd, *J* = 8.5, 0.5 Hz, 1H), 7.39 (dd, *J* = 8.5, 7.0 Hz, 1H), 6.81 – 6.71 (m, 3H), 6.69 (d, *J* = 1.8 Hz, 1H), 4.12 (t, *J* = 7.3 Hz, 2H), 3.82 (s, 3H), 3.68 (s, 3H), 3.02 (t, *J* = 7.5 Hz, 2H) ; ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.0, 149.0, 147.8, 139.4, 131.2, 130.9, 129.1, 128.7, 128.5, 126.7, 125.1, 124.3, 120.9, 120.3, 112.2, 111.4, 105.1, 56.0, 55.8, 42.2, 34.7; IR ν (neat) 2936, 1698, 1495, 1262, 1027 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{21}H_{19}NO_3$ 334,1438, found 334,1433.

Strain, growth conditions and measurement of minimal inhibitory concentration

The *Pseudomonas aeruginosa* strain used in this study is the PAO1 strain from CBSA lab collection. Naphtholactams **3** were solubilized in DMSO. The strain was cultured in LB medium at 37°C with, when indicated, addition of 3% DMSO, 2% Tween 80 and 300 µg/ml naphtholactams. Growth analysis was assessed by measuring the optical density of the culture at 600 nm (OD_{600}) and was performed in 96-well microplates (CytoOne) in a spectrophotometer (Tecan) with agitation. The MIC of naphtholactams were determined by microdilution method in accordance with the guidelines of the Clinical and Laboratory Standards Institute with the exception of growth medium. LB medium supplemented with 2% Tween 80 was used. Bacterial strains were added with an inoculum of 5.10^5 CFU/mL. Subsequent 2-fold serial dilutions of naphtholactams were performed to obtain concentrations ranging from 300 to 0.3 µg/ml. The MIC corresponds to the lowest concentration in the wells where no growth is observed.

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Supplementary Material

NMR spectra can be found online in the supplementary material.

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