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Graphical Abstract

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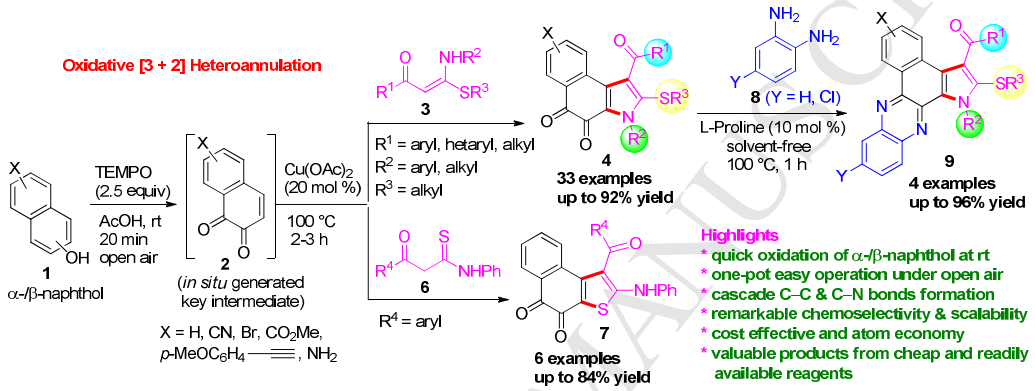

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1*H*-benzo[*a*]pyrrolo[3,2-*c*]phenazines

ABSTRACT

An operationally simple and efficient one-pot method for the synthesis of 1-aroyl (or alkanoyl)-2-thioalkyl-3-aryl (or alkyl)-3*H*-benzo[*e*]indole-4,5-diones and naphtho[2,1-*b*]thiophene-4,5-diones has been devised by copper-catalyzed cross-coupling of α-oxoketene *N*,*S*-acetals/β-ketothioamides with α-/β-naphthols in open air for the first time. The key to the success of this transformation is the room temperature oxidation of α-/β-naphthol to 1,2-naphthoquinone as a reactive species, which undergoes formal [3 + 2] annulation with α-oxoketene *N*,*S*-acetals/β-ketothioamides via cascade sequence of Michael addition/tautomerization/oxidation/cyclization/aromatization reactions, enabling addition of a pyrrole/thiophene ring onto naphthoquinone moiety. Further, benzo[*e*]indole-4,5-diones were transformed to pentacyclic fused phenazine derivatives under solvent-free conditions. Based on our experimental outcomes, a tentative mechanistic rationale for this chemoselective protocol is proposed, which is well validated and supported by the control experiments.

1. INTRODUCTION

The development of sustainable chemical processes has become a key research area providing solutions to important societal demands by optimizing the use of natural resources, and minimizing waste and environmental impact. Among the relevant methods for achieving this goal, catalysis represents a key and central approach. It is of great significance to effectively construct privileged molecules from synthetic chemistry and drug discovery viewpoints. Amongst nitrogen-containing fused heterocycles, indoles and their analogues are well recognized as privileged scaffolds prevalent in a vast array of natural products,[1] which find applications as pharmaceuticals and in agricultural chemicals.[2] Among benzo-fused indoles, benzo[*e*]indole and its analogues have recently drawn significant interest from industry and academia as a core architecture of many natural products and pharmacologically active compounds.[3] For example, benzo[*e*]indole serves as an important synthetic intermediate to generate hasubanan alkaloid hasubanonine.[3a] Also, 5-hydroxy-CBI-TMI has been utilized as a stable prodrug to construct cyclopropylindole antitumor agents and antibiotics.[3c] Further, benzo[*f*]indole-4,9-dione derivatives exhibit diversified biological activities such as antineoplastic, antibacterial, virus-static, fungicidic and anticoagulant properties.[4] Hence, the benzo-fused indole moiety has great potential for the generation of new biologically active molecules or therapeutic agents.

Given the synthetic and practical significance of these intriguing scaffolds, over the years, different strategies for the construction of benzo[*e*]indoles[5,6] and benzo[*f*]indole-4,9-diones[7] have been explored. Recently, a direct synthetic approach to access benzo[*e*]indoles by Diels-Alder reaction of 2-vinylpyrroles and arynes was developed.[8] Despite some notable recent achievements, the reported methods inevitably suffer from some clear disadvantages such as inaccessible starting materials,[3c,d] complicated procedures,[5] harsh reaction conditions,[6,7] and generation of undesired by-products, which limit their application to a certain extent. Considering these concerns, development of operationally simple and pot-/atom-/step-economic (PASE) methods utilizing readily available and inexpensive materials to access benzo-fused indoles and fundamental extension of their range are very much required, which would definitely complement the previously known strategies.

In this regard, the α-oxoketene *S*,*S*-acetals,[9] *N*,*O*-acetals[10] and *N*,*S*-acetals,[11] owing to their easy preparation, high stability and

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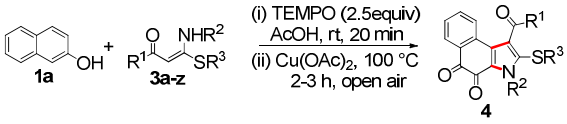
wonderful reactivity, have proven to be the fascinating and multipurpose synthons for the construction of diverse heterocyclic frameworks. However, to the best of our knowledge, no report is known to date on the synthesis of benzo-fused indole derivatives utilizing α-oxoketene *N*,*S*-acetals. Keeping the knowledge of benzo-fused indole syntheses[5-8] in mind, we reasonably envisioned that the α-oxoketene *N*,*S*-acetals behaving as enaminones could be utilized as three atoms (C-C-N) reaction partner. As a consequence, we hypothesized the possibility of annulation between 1,2-naphthoquinone (generated in situ from β-naphthol) and α-oxoketene *N*,*S*-acetal, in order to open new intriguing synthetic possibility for the construction of benzo-fused indole scaffold. Herein, we report a TEMPO mediated, copper-catalyzed one-pot synthesis of a broad array of 1-aroyl (or alkanoyl)-2-thioalkyl-3-aryl (or alkyl/cycloalkyl)-3*H*-benzo[*e*]indole-4,5-diones via oxidative formal [3 + 2] annulative coupling of α-oxoketene *N*,*S*-acetals with β-naphthols in a single operation (Scheme 1). Notably, the consecutive formation of C–C and C–N bonds enabled a pyrrole ring over naphthoquinone moiety empowering this strategy an excellent tool towards molecular diversity. However, the demand for better synthetic methods leading to bioactive scaffolds and their derivatives is still high and continuous. Of particular interest is the chemoselectivity of the reactions consistent with a cascade process.



3a: R^1=C_6H_5, R^2=C_6H_5, R^3=Me; **3b**: R^1=4-MeC_6H_4, R^2=C_6H_5, R^3=Me
3c: R^1=2-MeOC_6H_4, R^2=C_6H_5, R^3=Me; **3d**: R^1=2-ClC_6H_4, R^2=C_6H_5, R^3=Me
3e: R^1=2-BrC_6H_4, R^2=C_6H_5, R^3=Me; **3f**: R^1=2-furyl, R^2=C_6H_5, R^3=Me
3g: R^1=2-thienyl, R^2=C_6H_5, R^3=Me; **3h**:R^1=3-pyridyl, R^2=C_6H_5, R^3=Me
3i: R^1=1-naphthyl, R^2=C_6H_5, R^3=Me; **3j**: R^1=4-biphenyl, R^2=C_6H_5, R^3=Me
3k: R^1=cyclopropyl, R^2=C_6H_5, R^3=Me; **3l**:R^1=*iso*-butyl, R^2=C_6H_5, R^3=Et
3m: R^1=4-MeOC_6H_4, R^2=C_6H_5, R^3=Et; **3n**: R^1=4-BrC_6H_4, R^2=C_6H_5, R^3=Et
3o: R^1=4-ClC_6H_4, R^2=C_6H_5, R^3=*n*-Pr; **3p**:R^1=C_6H_5, R^2=C_6H_5, R^3=*n*-Bu
3q: R^1=4-BrC_6H_4, R^2=C_6H_5, R^3=Bn; **3r**: R^1=4-ClC_6H_4, R^2=C_6H_5, R^3=methallyl
3s: R^1=4-MeC_6H_4, R^2=Me, R^3=Et; **3t**: R^1=3-MeOC_6H_4, R^2=Me, R^3=Et
3u: R^1=3-BrC_6H_4, R^2=Me, R^3=Et; **3v**: R^1=C_6H_5, R^2=Me, R^3=Me;
3w: R^1=4-MeC_6H_4, R^2=cyclohexyl, R^3=Me; **3x**: R^1=4-ClC_6H_4,R^2=4-MeC_6H_4, R^3=Et
3y: R^1=C_6H_5, R^2=4-FC_6H_4, R^3=Me; **3z**: R^1=4-MeC_6H_4, R^2=1-naphthyl, R^3=Me

Scheme 1. One-pot synthesis of 3*H*-benzo[*e*]indole-4,5-diones **4**.

The metal-catalyzed cross coupling reactions[12] (MCCCR) have proven to be powerful strategies enabling realization of molecular diversity and synthetic versatility. They have profoundly changed the protocols for the construction of simple/complex molecules for organic materials, polymers and lead compounds in medicinal chemistry. Oxidative cross-coupling[13] (OCC) is a hot research topic that covers aspects of classical coupling, C–H functionalization, oxidation reactions, and radical chemistry for chemical, materials and biological synthesis. Indeed, it is well established that a copper-oxygen system[14] could be viewed as powerful reaction system for carbon–carbon and carbon–heteroatom bonds formation due to low toxicity, ease of handling and good functional group tolerance. Cascade processes[15] have received tremendous developments over the past decades, and remain one of the most powerful tools to create C–C and C–X (X = heteroatom) bonds in one-pot due to their ecologic and economic competence. These strategies are not only limited to the syntheses of simple molecules, but also have been utilized for the biomimetic synthesis of several natural products transforming the field dramatically.[16]

2. Results and discussion

Most of the reactions in organic chemistry are reagent- or catalyst-controlled reactions, and the regio- and stereoselectivity of these reactions are determined by the inherent nature of the reagent or catalyst. In sharp contrast, substrate-directed reactions determine the selectivity of the reactions by the functional group on the substrate, and can strictly distinguish sterically and electronically similar multiple reaction sites in the substrate. In this perspective, the rich and fascinating chemistry of α-oxoketene *N*,*S*-acetals with general formula **I** (Figure 1), features an unusual structure with electron-withdrawing and electron-donating functionalities (carbonyl, thioalkyl, and amino groups) attached to the two ends of the olefinic carbon–carbon bond. They exert amazing reactivity and emerged as novel multi-role-synthons for the construction of various heterocyclic systems and related useful frameworks.[17,18] On the other hand, cheap, easily available, and easy to handle β-naphthol has been well recognized as highly reactive reaction partner in various organic transformations.[19]

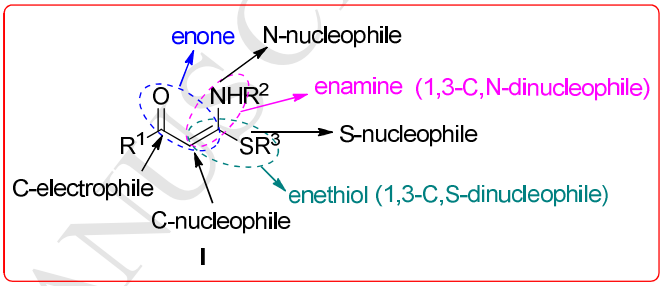


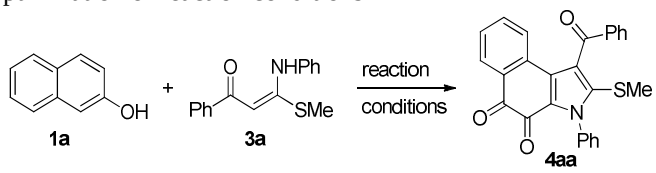
Figure 1. Reactivity profile of α-oxoketene *N*,*S*-acetals.

However, the synthetic utility of α-oxoketene *N*,*S*-acetals towards β-naphthol has not yet been reported, which could be an impetus for untold numbers of research projects. Recently, Li and co-workers[20] exploited *N*,*S*-ketene acetals for the direct construction of 2-aryliminochromenes. Inspired by above findings, and in continuation of our ongoing research toward the development of powerful synthetic strategies to assemble different heterocyclic scaffolds utilizing α-oxoketene *N*,*S*-acetals[21] as a good reaction partner, we turned our attention to utilize *N*,*S*-acetal and β-naphthol with the aim to generate hitherto unknown benzo-fused indole via one-pot cascade aza-annulation. To validate our hypothesis, we commenced our study employing β-naphthol (**1a**) and α-oxoketene *N*,*S*-acetal (**3a**) as model substrates to examine various reaction parameters. The results are summarized in Table 1.

At the outset of our study, we performed the model reaction of **1a** (0.5 mmol) with **3a** (0.5 mmol) in 3 mL of AcOH without any oxidant and catalyst at room temperature in open air. Disappointingly, we did not observe any trace of the desired product **4aa**, even after 12 h of stirring, and the starting materials remained completely unreacted (Table 1, entry 1). During the recent past, TEMPO has emerged as clean and mild oxidant that could be used to construct C–C/C–N bonds.[22] Therefore; we carried out the model reaction in the presence of 1 equiv of TEMPO at room temperature and at 100 °C, separately. Reaction failed under above both conditions (Table 1, entries 2 and 3). Keeping in mind the use of relatively inexpensive and less toxic copper salts[23] in organic synthesis, we performed the test reaction in the presence of 10 mol % of CuCl and 1 equiv of TEMPO at room temperature. Notably, CuCl triggered the reaction producing the desired product **4aa**, albeit in only 18% isolated yield (Table 1, entry 4). The above observation was encouraging enough to optimize the reaction conditions. To improve the yield

of **4aa**, we performed the reaction at higher temperature. We found that maximum conversion occurred at 100 °C, providing the desired product **4aa** in 44% yield (Table 1, entries 5 and 6). The improvement in the result of the protocol prompted us to investigate copper(II) salts such as $CuBr_2$, $Cu(OAc)_2$, $Cu(OTf)_2$, and $Cu(acac)_2$ (Table 1, entries 7-10). Among above screened copper salts, copper acetate showed better catalytic activity than other copper species (Table 1, entry 8).

Table 1
Optimization of reaction conditions[a]



Entry	Oxidant (equiv)	Catalyst (mol %)	Temp (^oC)	Time (h)	Yield[b] (%)
1	none	none	rt	12	NR
2	TEMPO (1)	none	rt	12	NR
3	TEMPO (1)	none	100	12	NR
4	TEMPO (1)	CuCl (10)	rt	12	18
5	TEMPO (1)	CuCl (10)	70	12	36
6	TEMPO (1)	CuCl (10)	100	12	44
7	TEMPO (1)	$CuBr_2$ (10)	100	10	56
8	TEMPO (1)	$Cu(OAc)_2$ (10)	100	5	72
9	TEMPO (1)	$Cu(OTf)_2$ (10)	100	7	60
10	TEMPO (1)	$Cu(acac)_2$ (10)	100	8	56
11	TEMPO (1)	$Cu(OAc)_2$ (20)	100	3	82
12	TEMPO (1)	$Cu(OAc)_2$ (30)	100	3	82
13	TEMPO (2.5)	$Cu(OAc)_2$ (20)	100	2	92
14	TEMPO (3)	$Cu(OAc)_2$ (20)	100	2	92
15	TEMPO (2.5)	$Cu(OAc)_2$ (20)	70	4	65
16	TEMPO (2.5)	$Cu(OAc)_2$ (20)	120	2	62
17	TBHP (2.5)	$Cu(OAc)_2$ (20)	100	6	32
18	$PhI(OAc)_2$ (2.5)	$Cu(OAc)_2$ (20)	100	6	26
19	Oxone (2.5)	$Cu(OAc)_2$ (20)	100	6	18
20	TEMPO (2.5)	$NiCl_2$ (20)	100	4	76
21	TEMPO (2.5)	$FeCl_3$ (20)	100	4	64
22	none	$Cu(OAc)_2$ (20)	100	12	NR

[a] Reaction conditions: All the reactions were performed with **1a** (0.5 mmol), **3a** (0.5 mmol) in 3 mL of AcOH in open air.

[b] Isolated yields.

NR = No reaction.

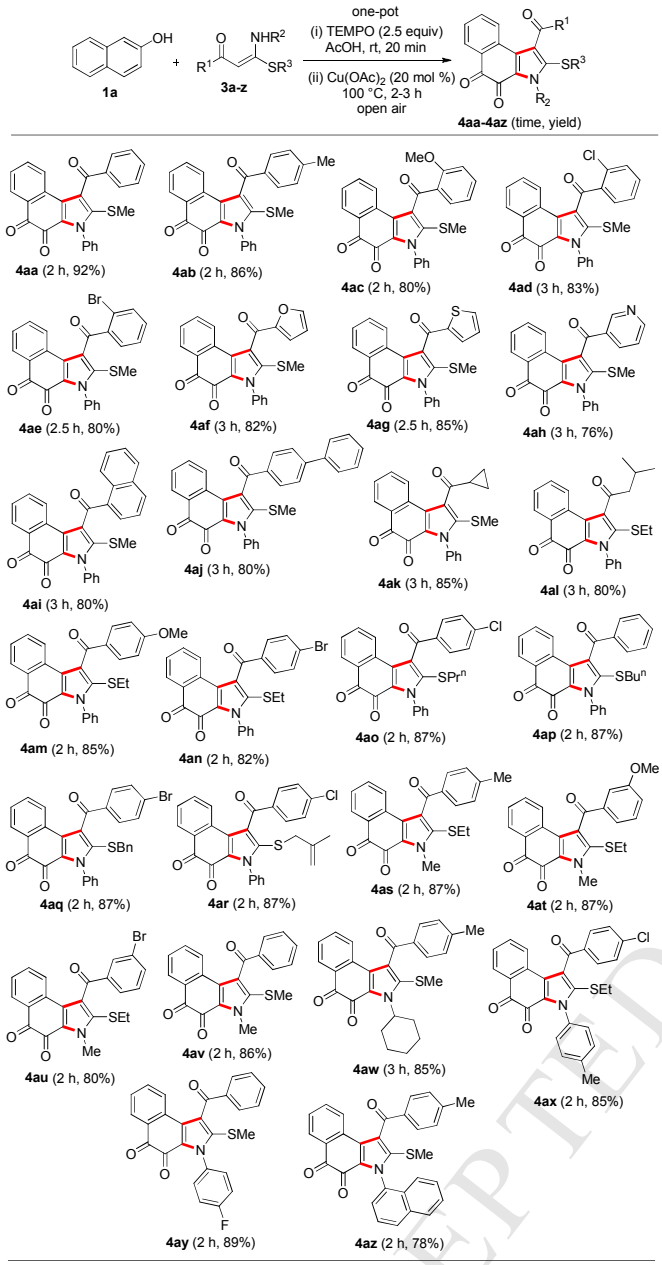
Observing the efficacy of $Cu(OAc)_2$, next we optimized its loading. It was found that 20 mol % of $Cu(OAc)_2$ furnished the best result providing the desired product **4aa** in 82% yield within 3 h (Table 1, entry 11). Further increasing the amount of $Cu(OAc)_2$ could not improve the result (Table 1, entry 12). Then, we screened the loading of TEMPO, and it was observed that 2.5 equiv of TEMPO afforded maximum conversion in minimum time providing the desired product **4aa** in 92% yield (Table 1, entries 13 and 14). Further, decreasing or increasing the temperature was found to be unfavorable to the reaction (Table 1, entries 15 and 16). Thus, 100 °C was found to be the optimum temperature for the appropriate yield of **4aa**. Some other oxidants such as *tert*-butyl hydroperoxide (TBHP), $PhI(OAc)_2$ and Oxone® were also evaluated but were found to be inferior to TEMPO (Table 1, entries 17-19). To check the generality of the protocol, we screened some other transition-metal catalysts such as $NiCl_2$ and $FeCl_3$. They also catalyzed the reaction but could not provide better result than $Cu(OAc)_2$ (Table 1, entries 20 and 21). Without TEMPO and with 20 mol % of $Cu(OAc)_2$ at 100 °C, the reaction did not occur (Table 1, entry 22), revealing the significance of TEMPO to the success of the reaction. Thus, the optimum condition for the synthesis of **4aa** was achieved by employing **1a** (0.5 mmol), **3a** (0.5 mmol), TEMPO (2.5 equiv), 20 mol % of $Cu(OAc)_2$, in 3 mL of AcOH at 100 °C in open air (Table 1, entry 13).

With the established optimal conditions in hand, we then set out to explore the generality of the protocol by using structurally diverse α-oxoketene *N*,*S*-acetals and β-naphthols. As shown in Tables 2 and 3, a myriad of *N*,*S*-acetals are successful substrates, providing the corresponding desired product **4** in good to excellent yield. To address the factors that determine the reaction outcome, the electronic and steric properties of the substituents R^1, R^2 and R^3 at α-oxoketene *N*,*S*-acetals were systematically varied. R^1 moiety as various aromatic groups with electron-donating and electron-withdrawing substituents, regardless of their positions, participated well in the reaction affording the corresponding 3*H*-benzo[*e*]indole-4,5-diones in high yields, revealing no obvious electronic impact (Table 2). The variants of the substituents like Me, OMe, Cl, and Br groups on the phenyl ring (R^1 moiety) were found to be compatible under the standard conditions (Table 2, **4ab**-**4ae** and **4am**-**4ar**). The introduction of halogen (e.g., chloro and bromo) substituents into target product is attractive because of their potential for further synthetic elaborations. Importantly, *N*,*S*-acetals bearing π-electron excessive groups such as 2-furyl and 2-thienyl as well as π-electron deficient 3-pyridyl substituent at R^1 moiety were also well tolerated under standard conditions resulting the corresponding products in high yields (Table 2, **4af**-**4ah**). It is noteworthy that *N*,*S*-acetals bearing not only aromatic and heteroaromatic groups at R^1 moiety, but extended aromatics such as 1-naphthyl and biphenyl groups were also found to be compatible well (Table 2, **4ai**, **4aj**). Notably, when R^1 was switched to alkyl substituent such as cyclopropyl and *iso*-butyl groups, the corresponding products **4ak** and **4al** were obtained in 85% and 80% yield, respectively.

Next, we evaluated the substrate **3** bearing different R^3 groups. Replacing the R^3 methyl group with substituents such as ethyl, *n*-propyl, *n*-butyl, benzyl and methallyl were successfully amenable to this protocol affording the corresponding 3*H*-benzo[*e*]indole-4,5-diones in high yields (Table 2, **4am**-**4ar**), revealing the broad adaptability of this method. The one-pot cascade strategy reported herein allows a novel entry to 1,2,3-trisubstituted-3*H*-benzo[*e*]indole-4,5-diones **4** with full regiocontrol on all the three positions of the newly formed pyrrole ring, which would otherwise be more difficult to prepare by alternative routes. In order to extend the substrate scope, we investigated the effect of R^2 on the efficacy of this protocol. For R^2 of α-oxoketene *N*,*S*-acetals, substituents such as alkyl and aryl groups could be tolerated well, resulting the desired products in high yields. Delightedly, when R^2 are alkyl substituents such as methyl and cyclohexyl groups, the corresponding products were obtained in good yields (Table 2, **4as**-**4aw**). When R^2 moieties are electron-donating 4-methylphenyl and electron-withdrawing 4-flurophenyl groups, the corresponding products were obtained in 85% and 89% yield, respectively (Table 2, **4ax** and **4ay**). Remarkably, switching R^2 as a 1-naphthyl group also worked well furnishing the desired product **4az** in 78% yield.

Table 2

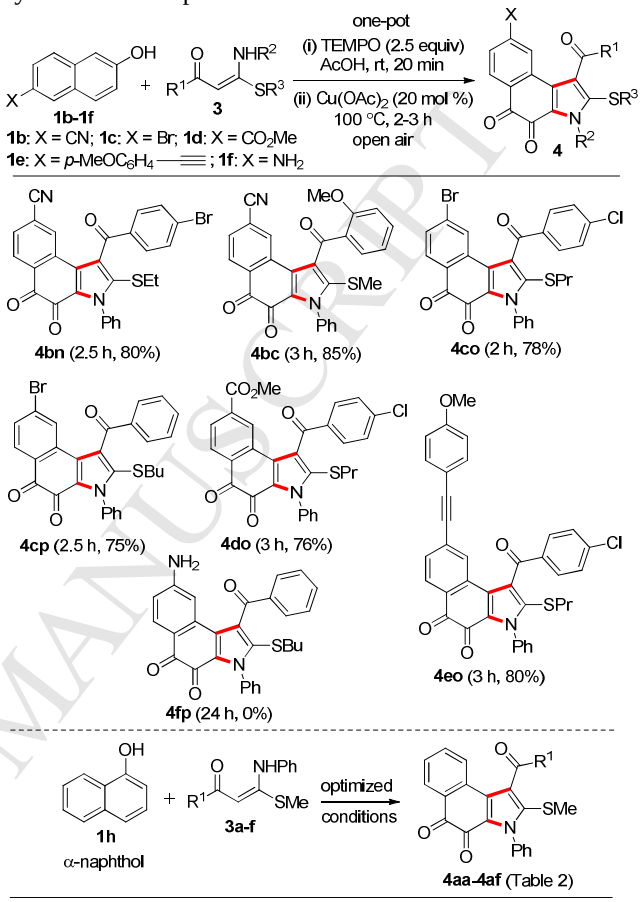
Scope of α-oxoketene *N*,*S*-acetals



To further extend the synthetic utility of this one-pot cascade reaction, we also investigated substituted β-naphthols **1b**-**1f** with a view to add further diversity to the benzene ring of 3*H*-benzo[*e*]indole-4,5-diones. The results demonstrated that substituted β-naphthols displayed similar reactivity as β-naphthol and took part in the reaction effectively to yield the desired products **4** in good yields (Table 3). Thus, substituted β-naphthols such as 6-cyano-2-naphthol **1b**, 6-bromo-2-naphthol **1c**, 6-carbomethoxy-2-naphthol **1d**, and 6-(*p*-methoxyphenylethynyl)-2-naphthol **1e** upon treatment with *N*,*S*-acetals under the previously described one-pot standard conditions, afforded 1,2,3,8-tetrasubstituted 3*H*-benzo[*e*]indole-4,5-diones in 76-85% yields (Table 3). This result greatly expanded the structural diversity of product **4**. However, 6-amino-β-naphthol **1f** did not proceed under standard conditions, thus limiting the scope of the reaction to some extent. To further demonstrate the general applicability of this coupling reaction, we used α-naphthol in place of β-naphthol. Treatment of α-naphthol **1h** instead of β-naphthol also generated the same 1,2-naphthoquinone **2** in the first step, which followed the similar sequence of reactions to afford the desired 3*H*-benzo[*e*]indole-4,5-diones **4** in high yields (Table 3). Thus, α-naphthol was also found to be equally facile towards this novel one-pot cascade protocol under standard conditions.

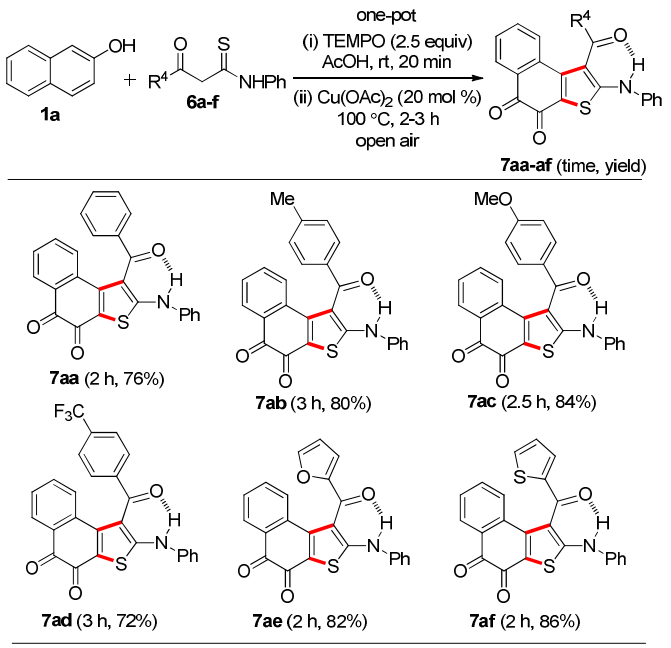
Table 3

Use of substituted β-naphthols and α-naphthol toward the synthesis of compounds **4**



To demonstrate the broad synthetic usefulness of our developed one-pot methodology, next we envisioned to utilize β-ketothioamide in place of *N*,*S*-acetal. Consequently, when β-ketothioamide **6a** was treated with β-naphthol **1a** under the previously described one-pot optimized conditions, entirely different scaffold 1-aroyl-2-(phenylamino)naphtho[2,1-*b*]thiophene-4,5-dione **7aa** was obtained in 76% yield (Table 4). The generality of the above reaction was established by synthesizing six naphtho[2,1-*b*]thiophene-4,5-diones (**7aa**-**7af**) utilizing different β-ketothioamides (**6a**-**6f**) under standard reaction conditions (Table 4). R^4 moiety of thioamide as various aromatic groups with electron-donating and electron-withdrawing substituents as well as heteroaromatic groups such as 2-furyl and 2-thienyl participated well in the reaction affording the corresponding product **7** in good yield (Table 4). Very recently, we synthesized 2,3-disubstituted naphtho[2,1-*b*]thiophene-4,5-diones by the reaction of α-enolic dithioesters with β-naphthols via cross-dehydrogenative thienannulation.[24] Heterocycle-fused naphthoquinones are common structural motifs in a large number of natural and synthetic products, which usually possess important biological activities such as anti-inflammatory and anti-cancer properties.[25]

Table 4
Synthesis of naphtho[2,1-*b*]thiophene-4,5-diones **7**



The structures of all the newly synthesized 3*H*-benzo[*e*]indole-4,5-diones **4** and naphtho[2,1-*b*]thiophene-4,5-diones **7** were fully characterized by their satisfactory spectral (^{1}H, ^{13}C, and HRMS) studies. Structure of one of the representative 1-cyclopropanecarbonyl-2-thiomethyl-3-phenyl-3*H*-benzo[*e*]indole-4,5-dione **4ak** was further unambiguously established by the single crystal X-ray diffraction analysis (Figure 2, see Supporting Information for details).

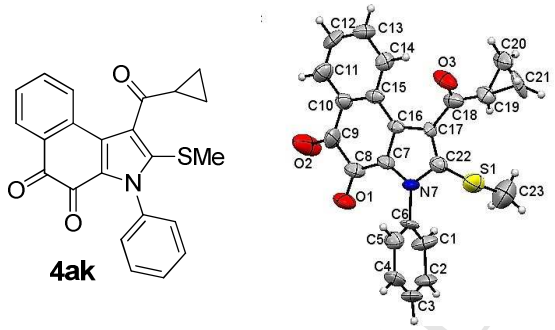
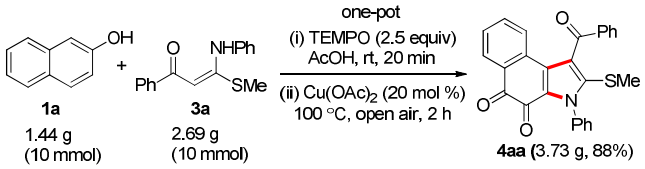


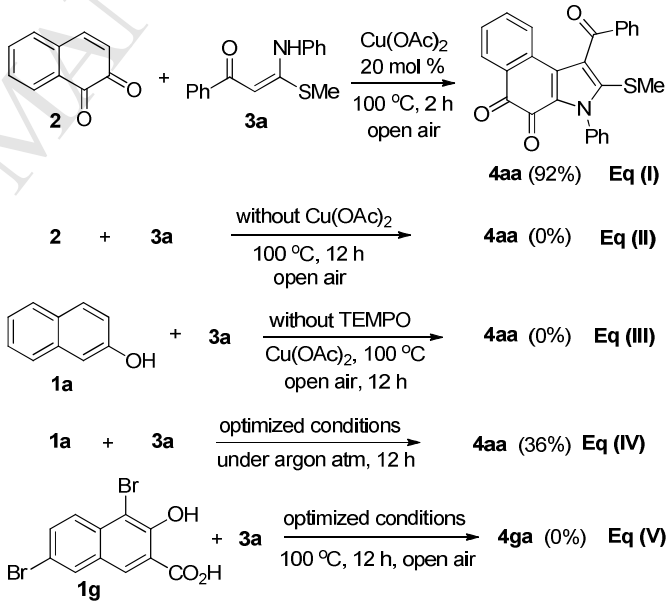
Figure 2. ORTEP diagram of compound **4ak** (CCDC No. 1570938).

To demonstrate the practical application and synthetic utility of the present protocol, we performed a gram-scale experiment with **1a** (10 mmol) and **3a** (10 mmol) under the optimal reaction conditions (Scheme 2). The desired product 1-benzoyl-2-thiomethyl-3-phenyl-3*H*-benzo[*e*]indole-4,5-dione **4aa** was obtained in 88% yield (3.73 g), which is comparable to the small scale experiment shown in Table 2 (92%). This result showed that the present method could be easily adopted for a large-scale preparation.



Scheme 2. Gram-scale synthesis of 3*H*-benzo[*e*]indole-4,5-dione **4aa**.

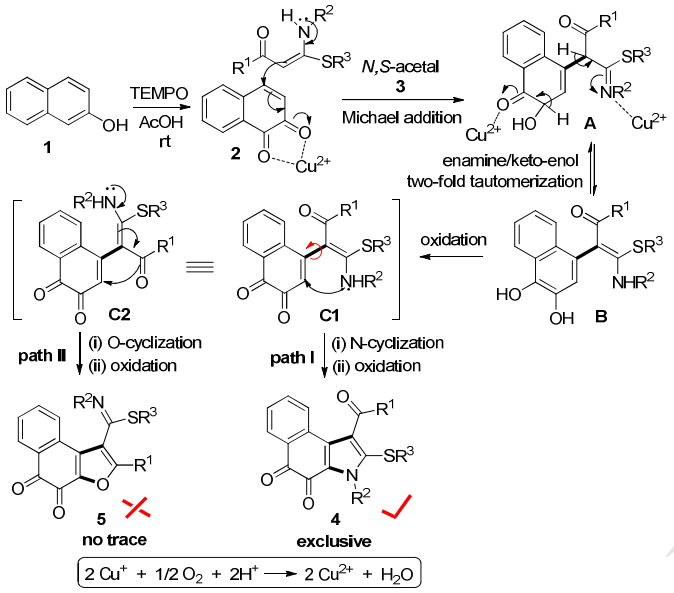
To define the possible intermediates and pathway, several control experiments were carried out, as shown in Scheme 3. First, we treated compound **2** with **3a** in the presence of 20 mol % of $Cu(OAc)_2$ at 100 °C in open air. Gratifyingly, the desired 3*H*-benzo[*e*]indole-4,5-dione **4aa** was obtained in 92% yield within 2 h (Scheme 3, Eq I), validating the intermediacy of 1,2-naphthoquinone **2** during the course of the reaction. The standard reaction of **2** with **3a** without $Cu(OAc)_2$ was unsuccessful even after 12 h (Scheme 3, Eq II). Similarly, another standard experiment of **1a** with **3a** without TEMPO could not provide the desired product **4aa** even after 12 h (Scheme 3, Eq III), suggesting the crucial role of TEMPO for the efficient oxidation of **1a** to **2** for successful transformation. To ascertain the role of the atmospheric oxygen during the transformation, we performed the standard reaction of **1a** with **3a** under the argon atmosphere. The much decreased yield (36%) of the desired product **4aa** under argon atmosphere indicated that the oxygen played an important accelerating role toward this transformation (Scheme 3, Eq IV). Finally, we treated both *ortho*-positions blocked β-naphthol **1g** with **3a** under optimized conditions. We did not observe any trace of the desired product **4ga**, even after 12 h of stirring, and the starting materials remained completely unreacted (Scheme 3, Eq V). The results of these control experiments revealed that the *in situ* generation of 1,2-naphthoquinone **2** as key intermediate is must for the progress of the reaction, and TEMPO, $Cu(OAc)_2$ as well as atmospheric oxygen are essential for the success of this protocol.



Scheme 3. Control experiments.

Based on literature reports and our experimental outcomes, a plausible mechanism for the formation of compounds **4** is depicted in Scheme 4. Considering the structural characteristics of this transformation, it could be suggested that the initial *in situ* oxidation of β-naphthol followed by a series of cascade reactions enabled 3*H*-benzo[*e*]indole-4,5-dione core **4**. The first step is believed to be a TEMPO mediated rapid oxidation of β-naphthol (**1**) to 1,2-naphthoquinone (**2**) that has been isolated and fully characterized. Then, Michael-type addition of α-carbon of *N*,*S*-acetal (**3**) to C4 of Cu^{2+}-complexed naphthoquinone (**2**) resulted into Michael adduct intermediate **A**, which eventually undergoes enamine and keto-enol two fold tautomerization to the thermodynamically more stable tautomer **B**. Subsequent oxidation of **B** by Cu(II), enabled the formation of enamine-

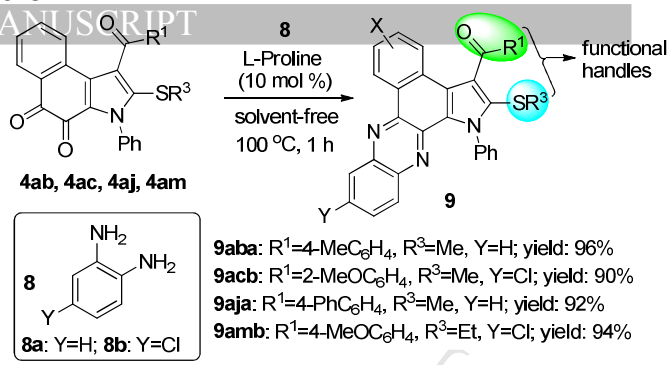
enone intermediate **C1**, which could probably undergo intramolecular cyclization via its possible two rotamers **C1** and **C2** through pathways I and II to furnish compounds **4** and **5**, respectively. The intermediate **C1** undergoes chemoselective N-cyclization *via* path I followed by oxidation to give the desired 3*H*-benzo[*e*]indole-4,5-dione **4** exclusively. The rotamer **C2** could lead to compound **5** by alternative O-cyclization *via* path II, which was not observed even in trace during our investigation. Here, $Cu(OAc)_2$ plays dual role as a Lewis acid to stabilize the structures of transition states *via* electrostatic interactions, and as oxidative catalyst. Molecular oxygen that acts as the terminal oxidant is involved in the oxidation of Cu(I) for the regeneration of Cu(II) to complete the catalytic cycle.



Scheme 4. Plausible mechanism for the formation of 3*H*-benzo[*e*]indole-4,5-diones **4**.

This method not only provides a new approach to tri- and tetra-substituted 3*H*-benzo[*e*]indole-4,5-diones, but also expands the application toward the synthesis of fused phenazine derivatives. To demonstrate the synthetic utility of the annulated products, further post functionalization was carried out. Since the 3*H*-benzo[*e*]indole-4,5-diones **4** bear two adjacent carbonyl groups as highly functional handles, we considered evaluating their scope with 1,2-diaminobenzenes[26] with a vision to install quinoxaline moiety onto benzo[*e*]indole-4,5-dione core to get fused phenazine derivatives. Phenazine derivatives have immense applications in various fields such as dyes, pharmaceuticals and antibiotics.[27]

Subsequently, we treated compound **4** with 1,2-diaminobenzenes **8** in the presence of 10 mol % of L-Proline at 100 °C under solvent-free conditions (for details in the optimization of conditions, refer to Supporting Information, Table S1). Differently decorated benzo[*e*]indole-4,5-diones **4ab**, **4ac**, **4aj** and **4am** could be successfully employed. The reaction proceeded smoothly affording the corresponding 1*H*-benzo[*a*]pyrrolo[3,2-*c*] phenazines in almost quantitative yields with a 6-6-6-6-5 pentacyclic core bearing aroyl and thioalkyl groups as functional handles for further modifications (Scheme 5, **9aba**, **9acb**, **9aja** and **9amb**).



Scheme 5. Synthetic application of compound **4**: Transformation to pentacyclic phenazine derivatives **9**.

3. Conclusion

In summary, a practical and reliable one-pot annulative coupling strategy has been developed for the direct synthesis of diverse 1,2,3-trisubstituted and 1,2,3,8-tetrasubstituted 3*H*-benzo[*e*]indole-4,5-diones from cheap and readily available α-/β-naphthols and α-oxoketene *N,S*-acetals in open air for the first time. This operationally simple domino [3 + 2] azaannulation features good atom and step economy, high yields and broad substrate scope. The reaction involved in situ generation of 1,2-naphthoquinone, the actual reactive species by the oxidation of α-/β-naphthol, which undergoes unique sequential functionalization with α-carbon atom and nitrogen atom of α-oxoketene *N,S*-acetal via Michael-type addition/tautomerization/oxidation/intramolecular cyclization/aromatization cascade sequence. This protocol not only allows the assembly of a huge range of benzo[*e*]indole-4,5-diones, but also expands the application towards the synthesis of naphtho[2,1-*b*]thiophene-4,5-diones employing β-ketothioamides instead of *N,S*-acetals, which are difficult to obtain otherwise. Further, the 3*H*-benzo[*e*]indole-4,5-dione frameworks undergo L-Proline-catalyzed cross-dehydrative coupling with *ortho*-phenylenediamines enabling pentacyclic 1*H*-benzo[*a*]pyrrolo[3,2-*c*]phenazine derivatives in excellent yields under solvent-free conditions. Notably, copper acetate plays dual role as a Lewis acid and oxidative catalyst, and atmospheric oxygen acts as the terminal green oxidant.

4. Experimental Section

4.1. General information

Unless otherwise noted, all reagents have been purchased from commercial suppliers and used without further purification. The α-oxoketene *N,S*-acetals[21a-c] and β-ketothioamides[21d,e] are not commercially sourced and were synthesized in good yields following the reported procedures. All the reactions were carried out in an oven-dried glassware under open air. Chromatograms were visualized by fluorescence quenching with UV light at 254 nm. ^{1}H and ^{13}C NMR spectra were recorded on NMR spectrophotometer operating at 500 and 125 MHz, respectively. Chemical shifts for ^{1}H and ^{13}C NMR spectra are reported as δ in units of parts per million (ppm) downfield from $SiMe_4$ (δ 0.0). Coupling constants (*J*) are given in Hz. Mass spectra were recorded under ESI/HRMS using ion trap mass analyzer. Melting points have been determined with Büchi B-540 melting point apparatus and are uncorrected.

*4.2. General procedure for the synthesis of compounds **4**.*

To the stirred solution of β-naphthol (0.5 mmol) in acetic acid (3 mL), TEMPO (2.5 equiv) was added at room temperature. With a stay of 20 minutes, 20 mol % of $Cu(OAc)_2$ was added followed by addition of *N,S*-acetal (0.5 mmol). The reaction mixture was heated at 100 °C till the completion of reaction (monitored by TLC). The reaction mixture was allowed to cool at room temperature followed by work up using ethyl acetate. The organic layer was dried over anhydrous Na_2SO_4, and solvent was evaporated under reduced pressure. The crude residue thus obtained was purified by column chromatography over silica gel (100-200 mesh) using hexane/ethyl acetate (17:3) as eluent to afford the pure desired products **4** (R_f = 0.40; hexane/ethyl acetate = 70/30).

*4.2.1. 1-Benzoyl-2-(methylthio)-3-phenyl-3H-benzo[e]indole-4,5-dione (**4aa**)*

A red solid (190.1 mg, 92% yield), R_f = 0.40 (hexane/ethyl acetate = 7:3). Mp: 199-201 °C. **^{1}H NMR** (500 MHz, $CDCl_3$): δ 8.06-8.04 (m, 2H), 8.02 (d, *J* = 7.65 Hz, 1H), 7.67-7.64 (m, 1H), 7.55-7.52 (m, 5H), 7.37-7.35 (m, 2H), 7.33-7.30 (m, 1H), 7.26-7.21 (m, 2H), 1.99 (s, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 194.2, 181.3, 168.0, 138.2, 137.4, 136.5, 135.4, 134.5, 131.9, 130.7, 130.0, 129.8, 129.6, 129.3, 129.2, 129.1, 128.4, 127.7, 126.5, 125.8, 19.5; **HRMS** (EI-TOF): calcd for $C_{26}H_{17}NNaO_3S$ $[M+Na]^+$: 446.0821, found: 446.0833.

*4.2.2. 1-(4-Methylbenzoyl)-2-(methylthio)-3-phenyl-3H-benzo[e]indole-4,5-dione (**4ab**)*

A red solid (190.3 mg, 86% yield), R_f = 0.40 (hexane/ethyl acetate = 7:3). Mp: 198-200 °C. **^{1}H NMR** (500 MHz, $CDCl_3$): δ 8.02 (d, *J* = 7.40 Hz, 1H), 7.95 (d, *J* = 8.15 Hz, 2H), 7.54-7.52 (m, 3H), 7.37-7.36 (m, 2H), 7.33-7.30 (m, 3H), 7.24-7.22 (m, 2H), 2.45 (s, 3H), 2.00 (s, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 193.7, 181.4, 167.9, 145.7, 138.1, 136.5, 135.3, 134.9, 131.9, 130.6, 130.1, 129.9, 129.9, 129.8, 129.5, 129.1, 129.1, 128.3, 127.6, 126.7, 125.7, 21.9, 19.4; **HRMS** (EI-TOF): calcd for $C_{27}H_{20}NO_3S$ $[M+H]^+$: 438.1158, found: 438.1166.

*4.2.3. 1-(2-Methoxybenzoyl)-2-(methylthio)-3-phenyl-3H-benzo[e]indole-4,5-dione (**4ac**)*

A red solid (170.2 mg, 80% yield), R_f = 0.40 (hexane/ethyl acetate = 7:3). Mp: 174-176 °C. **^{1}H NMR** (500 MHz, $CDCl_3$): δ 8.02 (d, *J* = 7.45 Hz, 1H), 7.88 (d, *J* = 7.10 Hz, 1H), 7.58-7.55 (m, 1H), 7.52-7.51 (m, 3H), 7.48 (d, *J* = 7.95 Hz, 1H), 7.38-7.35 (m, 1H), 7.32-7.30 (m, 2H), 7.27-7.24 (m, 1H), 7.09-7.06 (m, 1H), 7.01 (d, *J* = 8.40 Hz, 1H), 3.80 (s, 3H), 1.93 (s, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 192.9, 181.6, 168.0, 159.7, 137.8, 136.6, 135.2, 135.2, 132.2, 132.2, 130.4, 129.8, 129.7, 129.6, 129.4, 129.0, 128.2, 127.9, 127.7, 125.8, 120.7, 112.2, 56.0, 19.2; **HRMS** (EI-TOF): calcd for $C_{27}H_{19}NNaO_4S$ $[M+Na]^+$: 476.0927, found: 476.0933.

*4.2.4. 1-(2-Chlorobenzoyl)-2-(methylthio)-3-phenyl-3H-benzo[e]indole-4,5-dione (**4ad**)*

A red solid (191.3 mg, 83% yield), R_f = 0.40 (hexane/ethyl acetate = 7:3). Mp: 201-203 °C. **^{1}H NMR** (500 MHz, $CDCl_3$): δ 8.05 (d, *J* = 7.60 Hz, 1H), 7.79 (d, *J* = 7.70 Hz, 1H), 7.63 (d, *J* = 7.85 Hz, 1H), 7.52-7.50 (m, 5H), 7.46-7.43 (m, 1H), 7.40-7.38 (m, 1H), 7.32-7.30 (m, 3H), 1.87 (s, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 192.9, 181.2, 168.4, 138.1, 135.4, 133.5, 133.3, 131.9, 131.8, 131.2, 130.6, 129.5, 129.1, 128.6, 127.7, 127.0, 126.0, 19.3; **HRMS** (EI-TOF): calcd for $C_{26}H_{17}ClNO_3S$ $[M+H]^+$: 458.0612, found: 458.0613.

*4.2.5. 1-(2-Bromobenzoyl)-2-(methylthio)-3-phenyl-3H-benzo[e]indole-4,5-dione (**4ae**)*

A red solid (201.6 mg, 80% yield), R_f = 0.40 (hexane/ethyl acetate = 7:3). Mp: 185-187 °C. **^{1}H NMR** (500 MHz, $CDCl_3$): δ 8.04 (d, *J* = 7.45 Hz, 1H), 7.75 (d, *J* = 6.50 Hz, 1H), 7.71 (d, *J* = 7.65 Hz, 1H), 7.67 (d, *J* = 7.90 Hz, 1H), 7.52-7.51 (m, 3H), 7.45-7.37 (m, 3H), 7.31-7.30 (m, 3 H), 1.86 (s, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 193.6, 181.2, 168.5, 140.0, 139.4, 136.5, 135.5, 134.6, 133.3, 132.2, 131.9, 130.71, 129.9, 129.6, 129.2, 128.7, 127.7, 127.6, 126.2, 121.8, 29.7, 19.4; **HRMS** (EI-TOF): calcd for $C_{26}H_{17}BrNO_3S$ $[M+H]^+$: 502.0107, found: 502.0114.

*4.2.6. 1-(Furan-2-carbonyl)-2-(methylthio)-3-phenyl-3H-benzo[e]indole-4,5-dione (**4af**)*

A red solid (180.1 mg, 82% yield), R_f = 0.40 (hexane/ethyl acetate = 7:3). Mp: 196-198 °C. **^{1}H NMR** (500 MHz, $CDCl_3$): δ 8.13 (d, *J* = 8.15 Hz, 1H), 8.03 (d, *J* = 7.55 Hz, 1H), 7.76 (d, *J* = 8.30 Hz, 2H), 7.65 (d, *J* = 7.25 Hz, 2H), 7.55-7.53 (m, 1H), 7.49-7.46 (m, 1H), 7.42 (d, *J* = 7.40 Hz, 1H), 7.39-7.37 (m, 1H), 7.33 (d, *J* = 7.75 Hz, 1H), 7.28-7.26 (m, 1H), 2.03 (s, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 193.7, 181.4, 168.0, 147.2, 139.5, 138.2, 136.5, 136.1, 135.4, 132.0, 130.7, 130.6, 130.0, 129.90, 129.6, 129.2, 129.1, 128.6, 128.5, 127.7, 127.4, 126.6, 125.8, 19.6; **HRMS** (EI-TOF): calcd for $C_{24}H_{16}NO_4S$ $[M+H]^+$: 414.0795, found: 414.0829.

*4.2.7. 2-(Methylthio)-3-phenyl-1-(thiophene-2-carbonyl)-3H-benzo[e]indole-4,5-dione (**4ag**)*

A red solid (181.2 mg, 85% yield), R_f = 0.40 (hexane/ethyl acetate = 7:3). Mp: 195-197 °C. **^{1}H NMR** (500 MHz, $CDCl_3$): δ 8.03 (d, *J* = 7.95 Hz, 1H), 7.82 (d, *J* = 4.70 Hz, 1H), 7.71 (d, *J* = 3.70 Hz, 1H), 7.54-7.53 (m, 3H), 7.38-7.34 (m, 4H), 7.29-7.27 (m, 1H), 7.18-7.17 (m, 1H), 2.07 (s, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 185.7, 181.3, 167.9, 146.8, 144.8, 138.5, 136.4, 135.7, 135.4, 131.7, 130.6, 129.8, 129.6, 129.6, 129.1, 129.0, 128.8, 128.4, 127.6, 126.2, 125.7, 19.6; **HRMS** (EI-TOF): calcd for $C_{24}H_{16}NO_3S_2$ $[M+H]^+$: 430.0566, found: 430.0573.

*4.2.8. 2-(Methylthio)-1-nicotinoyl-3-phenyl-3H-benzo[e]indole-4,5-dione (**4ah**)*

A red solid (160.6 mg, 76% yield), R_f = 0.40 (hexane/ethyl acetate = 7:3). Mp: 105-107 °C. **^{1}H NMR** (500 MHz, $CDCl_3$): δ 9.19 (s, 1H), 8.86 (d, *J* = 3.80 Hz, 1H), 8.36 (d, *J* = 7.70 Hz, 1H), 8.05 (d, *J* = 7.55 Hz, 1H), 7.55-7.51 (m, 4H), 7.36-7.34 (m, 3H), 7.29 (d, *J* = 7.50 Hz, 1H), 7.23 (d, *J* = 7.80 HZ, 1H), 1.99 (s, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 192.9, 181.0, 168.1, 154.5, 151.5, 136.8, 136.3, 135.4, 132.9, 131.6, 130.9, 129.7, 129.3, 128.7, 127.6, 125.6, 124.0, 19.6; **HRMS** (EI-TOF): calcd for $C_{25}H_{16}N_2NaO_3S$ $[M+Na]^+$: 447.0774, found: 447.0774.

*4.2.9. 1-(1-Naphthoyl)-2-(methylthio)-3-phenyl-3H-benzo[e]indole-4,5-dione (**4ai**)*

A red solid (193.1 mg, 80% yield), R_f = 0.40 (hexane/ethyl acetate = 7:3). Mp: 102-104 °C. **^{1}H NMR** (500 MHz, $CDCl_3$): δ 9.20 (d, *J* = 8.60 Hz, 1H), 8.11 (d, *J* = 8.15 Hz, 1H), 8.04-7.97 (m, 3H), 7.79-7.76 (m, 1H), 7.66-7.64 (m, 1H), 7.53-7.45 (m, 5H), 7.37-7.35 (m, 2H), 7.29-7.26 (m, 1H), 7.25-7.22 (m, 1H), 1.87 (s, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 195.8, 181.4, 168.2, 138.8, 136.5, 135.5, 135.1, 134.7, 134.2, 133.1, 132.0, 131.0, 130.7, 130.1, 129.8, 129.6, 129.4, 129.2, 129.2, 128.8, 128.8, 128.5, 127.7, 127.1, 126.0, 125.8, 124.5, 19.4; **HRMS** (EI-TOF): calcd for $C_{30}H_{20}NO_3S$ $[M+H]^+$: 474.1158, found: 474.1152.

*4.2.10. 1-([1,1'-Biphenyl]-4-carbonyl)-2-(methylthio)-3-phenyl-3H-benzo[e]indole-4,5-dione (**4aj**)*

A red solid (201.9 mg, 80% yield), R_f = 0.40 (hexane/ethyl acetate = 7:3). Mp: 202-204 °C. **^{1}H NMR** (500 MHz, $CDCl_3$): δ 8.13 (d, *J* = 8.0 Hz, 2H), 8.03 (d, *J* = 7.35 Hz, 1H), 7.75 (d, *J* =

8.4 Hz, 2H), 7.65 (d, *J* = 7.6 Hz, 2H), 7.55-7.54 (m, 3H), 7.49-7.46 (m, 2H), 7.57 (d, *J* = 6.9 Hz, 1H), 7.39-7.37 (m, 1H), 7.35-7.32 (m, 1H), 7.27-7.26 (m, 3H), 2.02 (s, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 193.7, 181.4, 168.0, 147.2, 139.5, 138.2, 136.5, 136.0, 135.4, 131.9, 130.7, 130.6, 130.0, 129.8, 129.6, 129.2, 129.1, 128.6, 128.5, 127.7, 127.4, 126.6, 125.8, 19.6; **HRMS** (EI-TOF): calcd for $C_{32}H_{22}NO_3S$ $[M+H]^+$: 500.1315, found: 500.1322.

*4.2.11. 1-(Cyclopropanecarbonyl)-2-(methylthio)-3-phenyl-3H-benzo[e]indole-4,5-dione (**4ak**)*

A red solid (160.2 mg, 85% yield), R_f = 0.40 (hexane/ethyl acetate = 7:3). Mp: 195-197 °C. **^{1}H NMR** (500 MHz, $CDCl_3$): δ 8.05 (d, *J* = 7.60 Hz, 1H), 7.65 (d, *J* = 7.80 Hz, 1H), 7.53-7.52 (m, 4H), 7.35-7.29 (m, 3H), 2.57-2.52 (m, 1H), 2.17 (s, 3H), 1.47-1.45 (m, 2H), 1.22-1.20 (m, 2H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 203.3, 181.5, 168.2, 138.4, 136.7, 135.4, 132.2, 130.8, 130.0, 129.6, 129.2, 128.6, 127.7, 125.9, 24.5, 20.0, 13.9; **HRMS** (ESI/Q-TOF): calcd for $C_{23}H_{17}NNaO_3S$ $[M+Na]^+$: 410.0821, found: 410.0876.

*4.2.12. 2-(Ethylthio)-1-(3-methylbutanoyl)-3-phenyl-3H-benzo[e]indole-4,5-dione (**4al**)*

A red solid (170.6 mg, 80% yield), R_f = 0.40 (hexane/ethyl acetate = 7:3). Mp: 75-77 °C. **^{1}H NMR** (500 MHz, CDCl3): δ 8.05 (d, *J* = 7.70 Hz, 1H), 7.53-7.48 (m, 5H), 7.34-7.31 (m, 1H), 7.28-7.26 (m, 2H), 2.97 (d, *J* = 6.65 Hz, 2H), 2.50 (q, *J* = 7.38 Hz, 2H), 2.42-2.34 (m, 1H), 1.08-1.04 (m, 9H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 203.7, 181.3, 168.0, 136.5, 135.6, 135.3, 132.1, 130.7, 130.2, 129.8, 129.4, 129.0, 128.5, 127.8, 125.3, 54.5, 31.3, 24.4, 22.7, 14.7; **HRMS** (EI-TOF): calcd for $C_{25}H_{23}NNaO_3S$ $[M+Na]^+$: 440.1291, found: 440.1291.

*4.2.13. 2-(Ethylthio)-1-(4-methoxybenzoyl)-3-phenyl-3H-benzo[e]indole-4,5-dione (**4am**)*

A red solid (202.1 mg, 85% yield), R_f = 0.40 (hexane/ethyl acetate = 7:3). Mp: 185-187 °C. **^{1}H NMR** (500 MHz, $CDCl_3$): δ 8.02 (d, *J* = 8.20 Hz, 2H), 7.53-7.51 (m, 3H), 7.35-7.31 (m, 3H), 7.26-7.22 (m, 3H), 6.99 (d, *J* = 8.70 Hz, 2H), 3.89 (s, 3H), 2.41 (q, *J* = 7.31 Hz, 2H), 0.96 (t, *J* = 7.55 Hz, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 192.5, 181.5, 167.9, 164.7, 136.8, 136.6, 135.4, 132.5, 132.1, 130.6, 130.5, 129.8, 129.4, 129.2, 129.1, 128.3, 127.8, 127.6, 125.8, 114.3, 55.7, 30.8, 14.8; **HRMS** (ESI/Q-TOF): calcd for $C_{28}H_{21}NNaO_4S$ $[M+Na]^+$: 490.1083, found: 490.1085.

*4.2.14. 1-(4-Bromobenzoyl)-2-(ethylthio)-3-phenyl-3H-benzo[e]indole-4,5-dione (**4an**)*

A red solid (210.5 mg, 82% yield), R_f = 0.40 (hexane/ethyl acetate = 7:3). Mp: 208-210 °C. **^{1}H NMR** (500 MHz, $CDCl_3$): δ 8.03 (d, *J* = 7.50 Hz, 1H), 7.90 (d, *J* = 8.30 Hz, 2H), 7.66 (d, *J* = 8.40 Hz, 2H), 7.53-7.51 (m, 3H), 7.35-7.32 (m, 3H), 7.27 (d, *J* = 7.35 Hz, 1H), 7.19 (d, *J* = 7.80 Hz, 1H), 2.38 (q, *J* = 7.43 Hz, 2H), 0.95 (t, *J* = 7.52 Hz, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 193.2, 181.2, 168.0, 136.9, 136.4, 136.2, 135.4, 132.5, 131.8, 131.4, 130.8, 129.9, 129.9, 129.8, 129.6, 129.4, 129.1, 128.6, 127.8, 126.8, 125.6, 30.9, 29.7, 14.7; **HRMS** (ESI/Q-TOF): calcd for $C_{27}H_{18}BrNNaO_3S$ $[M+Na]^+$: 538.0083, found: 538.0083.

*4.2.15. 1-(4-Chlorobenzoyl)-3-phenyl-2-(propylthio)-3H-benzo[e]indole-4,5-dione (**4ao**)*

A red solid (217.2 mg, 87% yield), R_f = 0.40 (hexane/ethyl acetate = 7:3). Mp: 212-214 °C. **^{1}H NMR** (500 MHz, $CDCl_3$): δ 8.03 (d, *J* = 7.55 Hz, 1H), 7.98 (d, *J* = 8.45 Hz, 2H), 7.53-7.49 (m, 5H), 7.35-7.32 (m, 3H), 7.27 (d, *J* = 7.55 Hz, 1H), 7.20 (d, *J* = 7.55 Hz, 1H), 2.33 (t, *J* = 7.17 Hz, 2H), 1.29-1.26 (m, 2H), 0.66 (t, *J* = 7.20 Hz, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 193.0, 181.3, 168.0, 141.1, 137.3, 136.4, 135.8, 135.4, 131.8, 131.3, 130.8, 129.8, 129.6, 129.4, 129.1, 128.5, 127.8, 125.6, 38.6, 22.8, 12.8; **HRMS** (EI-TOF): calcd for $C_{28}H_{20}ClNNaO_3S$ $[M+Na]^+$: 508.0745, found: 508.0897.

*4.2.16. 1-Benzoyl-2-(butylthio)-3-phenyl-3H-benzo[e]indole-4,5-dione (**4ap**)*

A red solid (200.5 mg, 87% yield), R_f = 0.40 (hexane/ethyl acetate = 7:3). Mp: 141-143 °C. **^{1}H NMR** (500 MHz, $CDCl_3$): δ 8.05-8.02 (m, 3H), 7.67-7.64 (m, 1H), 7.54-7.52 (m, 5H), 7.35-7.30 (m, 3H), 7.24-7.22 (m, 2H), 2.35 (t, *J* = 7.30 Hz, 2H), 1.25-1.18 (m, 2H), 1.08-1.01 (m 2H), 0.69 (t, *J* = 7.25 HZ, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 194.1, 181.4, 167.9, 137.4, 137.3, 136.4, 135.3, 134.3, 131.9, 130.6, 129.9, 129.4, 129.0, 129.0, 128.3, 127.8, 127.1, 125.7, 36.2, 31.4, 21.3, 13.3; **HRMS** (EI-TOF): calcd for $C_{29}H_{23}NNaO_3S$ $[M+Na]^+$: 488.1291, found: 488.1309.

*4.2.17. 2-(Benzylthio)-1-(4-bromobenzoyl)-3-phenyl-3H-benzo[e]indole-4,5-dione (**4aq**)*

A red solid (250.9 mg, 87% yield), R_f = 0.40 (hexane/ethyl acetate = 7:3). Mp: 206-208 °C. **^{1}H NMR** (500 MHz, $CDCl_3$): δ 8.03 (d, *J* = 7.55 Hz, 1H), 7.85 (d, *J* = 8.50 Hz, 2H), 7.64 (d, *J* = 8.45 Hz, 2H), 7.50-7.47(m, 1H), 7.42-7.39 (m, 2H), 7.35-7.32 (m, 1H), 7.27 (d, *J* = 7.60 Hz, 1H), 7.20-7.13 (m, 4H), 6.93 (d, *J* = 7.75 Hz, 2H), 6.88 (d, *J* = 7.10 Hz, 2H), 3.65 (s, 2H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 193.1, 181.2, 168.0, 136.2, 136.1, 136.0, 135.4, 132.4, 131.8, 131.3, 130.8, 129.9, 129.8, 129.8, 129.4, 129.2, 128.9, 128.9, 128.7, 128.5, 127.8, 127.1, 125.8, 41.48; **HRMS** (EI-TOF): calcd for $C_{32}H_{20}BrNNaO_3S$ $[M+Na]^+$: 600.0239, found: 600.0210.

*4.2.18. 1-(4-Chlorobenzoyl)-2-((2-methylallyl)thio)-3-phenyl-3H-benzo[e]indole-4,5-dione (**4ar**)*

A red solid (200.5 mg, 80% yield), R_f = 0.40 (hexane/ethyl acetate = 7:3). Mp: 159-161 °C. **^{1}H NMR** R (500 MHz, $CDCl_3$): δ 8.03 (d, *J* = 7.60 Hz, 1H), 7.99 (d, *J* = 8.50 Hz, 2H), 7.52-7.48 (m, 5H), 7.34-7.31 (m, 3H), 7.27-7.24 (m, 1H), 7.17 (d, *J* = 7.60 Hz, 1H), 4.63 (d, *J* = 10.55 Hz, 2H), 2.98 (s, 2H), 1.30 (s, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 192.7, 181.3, 168.1, 141.0, 140.0, 136.4, 136.1, 135.8, 135.4, 131.8, 131.4, 130.7, 129.8, 129.8, 129.5, 129.4, 129.2, 129.0, 128.5, 128.1, 127.3, 125.8, 115.4, 44.4, 20.4; **HRMS** (EI-TOF): calcd for $C_{29}H_{21}ClNO_3S$ $[M+H]^+$: 498.0925, found: 498.0931.

*4.2.19. 3-Methyl-1-(4-methylbenzoyl)-2-(methylthio)-3H-benzo[e]indole-4,5-dione (**4as**)*

A red solid (170.2 mg, 87% yield), R_f = 0.40 (hexane/ethyl acetate = 7:3). Mp: 186-188 °C. **^{1}H NMR** (500 MHz, $CDCl_3$): δ 8.02 (d, *J* = 7.55 Hz, 1H), 7.85 (d, *J* = 8.20 Hz, 2H), 7.28-7.27 (m, 3H), 7.22-7.19 (m, 1H), 7.13 (d, *J* = 7.90 Hz, 1H), 4.11 (s, 3H), 2.72 (q, *J* = 7.46 Hz, 2H), 2.42 (s, 3H), 1.16 (t, *J* = 7.40 Hz, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 193.9, 181.6, 169.1, 145.5, 136.4, 135.4, 134.9, 132.2, 130.6, 130.1, 129.7, 129.6, 129.3, 128.8, 128.1, 127.4, 125.7, 34.0, 31.5, 21.9, 15.0; **HRMS** (EI-TOF): calcd for $C_{23}H_{19}NNaO_3S$ $[M+Na]^+$: 412.0978, found: 412.0991.

*4.2.20. 2-(Ethylthio)-1-(3-methoxybenzoyl)-3-methyl-3H-benzo[e]indole-4,5-dione (**4at**)*

A red solid (170.6 mg, 87% yield), R_f = 0.40 (hexane/ethyl acetate = 7:3). Mp: 147-149 °C. **^{1}H NMR** (500 MHz, $CDCl_3$): δ 8.03 (d, *J* = 7.50 Hz, 1H), 7.57 (s, 1H), 7.44 (d, *J* = 7.50 Hz, 1H), 7.37-7.33 (m, 1H), 7.30-7.27 (m, 1H), 7.24-7.21 (m, 1H), 7.17 (d, *J* = 6.50 Hz, 1H), 7.12 (d, *J* = 7.65 Hz, 1H), 4.12 (s, 3H), 3.87 (s, 3H), 2.73 (q, *J* = 7.31 Hz, 2H), 1.17 (t, *J* = 7.40 Hz, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 194.1, 181.5, 169.1, 160.1, 138.7, 136.5, 135.4, 132.1, 130.6, 130.0, 129.7, 129.4, 128.8, 128.2,

127.2, 125.7, 123.2, 120.9, 113.3, 55.6, 34.0, 31.5, 15.0; **HRMS** (EI-TOF): calcd for $C_{23}H_{19}NNaO_4S$ $[M+Na]^+$: 428.0927, found: 428.0928.

*4.2.21. 1-(3-Bromobenzoyl)-2-(ethylthio)-3-methyl-3H-benzo[e]indole-4,5-dione (**4au**)*

A red solid (183.0 mg, 80% yield), Rf = 0.40 (hexane/ethyl acetate = 7:3). Mp: 163-165 °C. **^{1}H NMR** (500 MHz, $CDCl_3$): δ 8.13 (s, 1H), 8.05 (d, *J* = 7.50 Hz, 1H), 7.83 (d, *J* = 7.65 Hz, 1H), 7.75 (d, *J* = 7.70 Hz, 1H), 7.37-7.30 (m, 2H), 7.24 (d, *J* = 7.85 Hz, 1H), 7.11 (d, *J* = 7.71 Hz, 1H), 4.12 (s, 3H), 2.73 (q, *J* = 7.05 Hz, 2H), 1.17 (t, *J* = 7.17 Hz, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 193.0, 181.3, 169.2, 139.2, 137.1, 136.5, 135.4, 132.4, 131.9, 130.7, 130.5, 129.7, 129.4, 129.0, 128.7, 128.4, 126.3, 125.5, 123.4, 34.1, 31.6, 14.9; **HRMS** (EI-TOF): calcd for $C_{22}H_{17}BrNO_3S$ $[M+H]^+$: 454.0107, found: 454.0113.

*4.2.22. 1-Benzoyl-3-methyl-2-(methylthio)-3H-benzo[e]indole-4,5-dione (**4av**)*

A red solid (160.2 mg, 86% yield), Rf = 0.40 (hexane/ethyl acetate = 7:3). Mp: 167-169 °C. **^{1}H NMR** (500 MHz, $CDCl_3$): δ 8.03-7.96 (m, 3H), 7.65-7.62 (m, 1H), 7.51-7.42 (m, 2H), 7.29-7.20 (m, 2H), 7.12 (d, *J* = 7.60 Hz, 1H), 4.12 (s, 3H), 2.26 (s, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 194.2, 181.4, 169.1, 137.7, 137.3, 135.3, 134.3, 132.0, 130.5, 129.8, 128.9, 128.1, 126.3, 125.6, 33.8, 19.5; **HRMS** (EI-TOF): calcd for $C_{21}H_{16}NO_3S$ $[M+H]^+$: 362.0845, found: 362.0854.

*4.2.23. 3-Cyclohexyl-1-(4-methylbenzoyl)-2-(methylthio)-3H-benzo[e]indole-4,5-dione (**4aw**)*

A red solid (190.5 mg, 85% yield), Rf = 0.40 (hexane/ethyl acetate = 7:3). Mp: 116-118 °C. **^{1}H NMR** (500 MHz, $CDCl_3$): δ 8.01 (d, *J* = 7.50 Hz, 1H), 7.86 (d, *J* = 7.80 Hz, 2H), 7.29-7.28 (m, 3H), 7.21-7.18 (m, 1H), 7.13 (d, *J* = 7.60 Hz, 1H), 2.64-2.62 (m, 2H), 2.43 (s, 3H), 2.27 (s, 3H), 1.95-1.93 (m, 2H), 1.71 (br, 3H), 1.45-1.42 (m, 3H), 0.89-0.84 (m, 1H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 194.3, 181.5, 166.0, 145.5, 135.3, 130.3, 130.0, 130.0, 129.7, 129.5, 128.0, 125.6, 58.9, 26.2, 21.8; **HRMS** (EI-TOF): calcd for $C_{27}H_{26}NO_3S$ $[M+H]^{+\cdot}$ 444.1628, found: 444.1637.

*4.2.24. 1-(4-Chlorobenzoyl)-2-(ethylthio)-3-(p-tolyl)-3H-benzo[e]indole-4,5-dione (**4ax**)*

A red solid (210.2 mg, 89% yield), Rf = 0.40 (hexane/ethyl acetate = 7:3). Mp: 223-225 °C. **^{1}H NMR** (500 MHz, $CDCl_3$): δ 8.03 (d, *J* = 7.60 Hz, 1H), 7.98 (d, *J* = 8.55 Hz, 2H), 7.49 (d, *J* = 8.45 Hz, 2H), 7.33-7.31 (m, 3H), 7.27-7.24 (m, 1H), 7.21 (d, *J* = 8.05 Hz, 2H), 7.18 (d, *J* = 8.10 Hz, 1H), 2.46 (s, 3H), 2.40 (q, *J* = 7.50 Hz, 2H), 0.96 (t, *J* = 7.20 Hz, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 193.0, 181.3, 168.0, 141.0, 139.7, 136.9, 135.8, 135.4, 133.8, 131.8, 131.3, 130.7, 129.8, 129.4, 128.5, 127.4, 126.7, 125.6, 30.9, 21.4, 14.7; **HRMS** (ESI/Q-TOF): calcd for $C_{28}H_{20}ClNNaO_3S$ $[M+Na]^+$: 508.0745, found: 508.0741.

*4.2.25. 1-Benzoyl-3-(4-fluorophenyl)-2-(methylthio)-3H-benzo[e]indole-4,5-dione (**4ay**)*

A red solid (201.7 mg, 89% yield), Rf = 0.40 (hexane/ethyl acetate = 7:3). Mp: 162-164 °C. **^{1}H NMR** (500 MHz, $CDCl_3$): δ 8.05-8.02 (m, 3H), 7.68-7.65 (m, 1H), 7.55-7.52 (m, 2H), 7.37-7.30 (m, 3H), 7.27-7.20 (m, 4H), 2.01 (s, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 194.0, 181.2, 168.1, 162.9 (d, *JC*-F = 248.65 Hz, Cipso), 138.3, 137.3, 135.4, 134.6, 132.3, 131.7, 130.7, 130.1, 130.0, 129.8, 129. 6 (d, *JC*-CCF = 8.96 Hz), 129.3, 129.1, 128.6, 126.7, 125.8, 116.3 (d, *JC*-CF = 22.97 Hz), 19.5; **HRMS** (EI-TOF): calcd for $C_{26}H_{17}FNO_3S$ $[M+H]^+$: 442.0908, found: 442.0913.

*4.2.26. 1-(4-Methylbenzoyl)-2-(methylthio)-3-(naphthalen-1-yl)-3H-benzo[e]indole-4,5-dione (**4az**)*

A red solid (190.2 mg, 78% yield), Rf = 0.40 (hexane/ethyl acetate = 7:3). Mp: 108-110 °C. **^{1}H NMR** (500 MHz, $CDCl_3$): δ 8.05 (d, *J* = 8.25 Hz, 1H), 8.03-8.00 (m, 2H), 7.97 (d, *J* = 8.10 Hz, 1H), 7.63-7.60 (m, 1H), 7.55-7.47 (m, 4H), 7.36-7.33 (m, 3H), 7.30-7.27 (m, 3H), 2.46 (s, 3H), 1.92 (s, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 193.7, 181.1, 167.5, 145.7, 135.3, 134.9, 134.1, 133.5, 132.6, 131.9, 131.8, 130.6, 130.5, 130.2, 130.1, 130.0, 129.9, 129.8, 129.3, 128.9, 128.6, 128.4, 127.8, 126.7, 126.6, 125.7, 125.7, 125.1, 121.5, 21.92, 20.21; **HRMS** (EI-TOF): calcd for $C_{31}H_{21}NNaO_3S$ $[M+Na]^+$: 510.1134, found: 510.1146.

*4.2.27. 1-(4-Bromobenzoyl)-2-(ethylthio)-4,5-dioxo-3-phenyl-4,5-dihydro-3H-benzo[e]indole-8-carbonitrile (**4bn**)*

A red solid (220.4 mg, 80% yield), Rf = 0.40 (hexane/ethyl acetate = 7:3). Mp: 279-281 °C. **^{1}H NMR** (500 MHz, $CDCl_3$): δ 8.08 (d, *J* = 8.15 Hz, 1H), 7.90 (d, *J* = 8.45 Hz, 2H), 7.68-7.67 (m, 3H), 7.63 (s, 1H), 7.55-7.53 (m, 3H), 7.35-7.33 (m, 2H), 2.41 (q, *J* = 7.33 Hz, 2H), 0.96 (t, *J* = 7.22 Hz, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 192.9, 180.7, 167.4, 167.2, 139.2, 138.0, 136.2, 132.6, 132.2, 131.8, 131.3, 131.0, 130.1, 129.7, 129.2, 127.7, 127.3, 126.7, 124.6, 30.9, 14.7; **HRMS** (EI-TOF): calcd for $C_{28}H_{17}BrN_2NaO_3S$ $[M+Na]^+$: 563.0035, found: 563.0035

*4.2.28. 1-(2-Methoxybenzoyl)-2-(methylthio)-4,5-dioxo-3-phenyl-4,5-dihydro-3H-benzo[e]indole-8-carbonitrile (**4bc**)*

A red solid (200.9 mg, 85% yield), Rf = 0.40 (hexane/ethyl acetate = 7:3). Mp: 187-189 °C. **^{1}H NMR** (500 MHz, $CDCl_3$): δ 8.09 (d, *J* = 7.80 Hz, 1H), 7.79 (dd, *J*1 = 1.55 Hz, *J*2 = 7.70 Hz, 1H), 7.77 (s, 1H), 7.61-7.57 (m, 1H), 7.56-7.51 (m, 4H), 7.32-7.30 (m, 2H), 7.10-7.07 (m, 1H), 7.04 (d, *J* = 8.40 Hz, 1H), 3.86 (s, 3H), 1.99 (s, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 192.2, 180.7, 166.9, 159.5, 139.5, 136.3, 135.5, 133.2, 131.9, 131.4, 130.5, 129.8, 129.3, 129.3, 128.0, 127.6, 120.9, 118.4, 117.5, 112.2, 56.1, 19.4; **HRMS** (EI-TOF): calcd for $C_{28}H_{19}N_2O_4S$ $[M+H]^+$: 479.1060, found: 479.1060.

*4.2.29. 8-Bromo-1-(4-chlorobenzoyl)-3-phenyl-2-(propylthio)-3H-benzo[e]indole-4,5-dione (**4co**)*

A red solid (221.5 mg, 78% yield), Rf = 0.40 (hexane/ethyl acetate = 7:3). Mp: 261-263 °C. **^{1}H NMR** (500 MHz, $CDCl_3$): δ 7.97 (d, *J* = 8.25 Hz, 2H), 7.87 (d, *J* = 8.10 Hz, 1H), 7.54-7.51 (m, 5H), 7.41 (d, *J* = 8.35 Hz, 1H), 7.36-7.33 (m, 3H), 2.34 (t, *J* = 7.12 Hz, 2H), 1.30-1.25 (m, 2H), 0.67 (t, *J* = 7.30 Hz, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 192.5, 180.4, 167.6, 141.2, 137.9, 136.2, 135.8, 133.3, 131.9, 131.6, 131.2, 131.0, 129.7, 129.5, 129.2, 128.8, 128.4, 127.7, 126.7, 38.6, 22.8, 12.8; **HRMS** (EI-TOF): calcd for $C_{28}H_{20}BrClNO_3S$ $[M+H]^+$: 564.0030, found: 564.0036

*4.2.30. 1-(4-Chlorobenzoyl)-8-((4-methoxyphenyl)ethynyl)-3-phenyl-2-(propylthio)-3H-benzo[e]indole-4,5-dione (**4eo**)*

A red solid (250.0 mg, 80% yield), Rf = 0.40 (hexane/ethyl acetate = 7:3). Mp: 201-203 °C. **^{1}H NMR** (500 MHz, $CDCl_3$): δ 8.00 (d, *J* = 7.90 Hz, 3H), 7.53-7.50 (m, 5H), 7.40 (d, *J* = 8.40 Hz, 2H), 7.37-7.34 (m, 3H), 7.28 (s, 1H), 6.89 (d, *J* = 8.40 Hz, 2H), 3.84 (s, 3H), 2.34 (t , *J* = 7.12 Hz, 2H), 1.30-1.26 (m, 2H), 0.67 (t, *J* = 7.20 Hz, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 192.7, 180.5, 168.0, 160.4, 141.0, 137.5, 136.4, 136.0, 133.5, 131.8, 131.3, 131.1, 131.1, 130.7, 129.6, 129.4, 129.2, 129.1, 128.4, 128.3, 127.8, 126.7, 114.2, 95.2, 87.4, 55.4, 38.6, 22.8, 12.8;

HRMS (EI-TOF): calcd for $C_{37}H_{26}ClNNaO_4S$ $[M+Na]^+$: 638.1163, found: 638.1163.

*4.2.31. 1-Benzoyl-8-bromo-2-(butylthio)-3-phenyl-3H-benzo[e]indole-4,5-dione (**4cp**)*

A red solid (201.0 mg, 75% yield), Rf = 0.40 (hexane/ethyl acetate = 7:3). Mp: 186-188 °C. **^{1}H NMR** (500 MHz, $CDCl_3$): δ 8.03 (d, *J* = 7.15 Hz, 2H), 7.85 (d, *J* = 8.50 Hz, 1H), 7.69-7.66 (m, 1H), 7.55-7.52 (m, 5H), 7.39-7.33 (m, 4H), 2.37 (t, *J* = 7.50 Hz, 2H), 1.25-1.19 (m, 2H), 1.09-1.02 (m, 2H), 0.70 (t, *J* = 7.22 Hz, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 193.6, 180.5, 167.5, 138.0, 137.3, 136.3, 134.4, 133.3, 131.7, 131.4, 130.9, 129.8, 129.5, 129.1, 128.9, 128.3, 127.7, 127.2, 36.3, 31.3, 21.3, 13.3; **HRMS** (EI-TOF): calcd for $C_{29}H_{22}BrNNaO_3S$ $[M+Na]^+$: 566.0396, found: 566.0396.

*4.2.32. Methyl 1-(4-chlorobenzoyl)-4,5-dioxo-3-phenyl-2-(propylthio)-4,5-dihydro-3H-benzo[e]indole-8-carboxylate (**4do**)*

A red solid (212.6 mg, 76% yield), Rf = 0.40 (hexane/ethyl acetate = 7:3). Mp: 227-229 °C. **^{1}H NMR** (500 MHz, $CDCl_3$): δ 8.08 (d, *J* = 7.80 Hz, 1H), 8.01 (d, *J* = 8.45 Hz, 2H), 7.90-7.88 (m, 1H), 7.82 (s, 1H), 7.55-7.53 (m, 3H), 7.50 (d, *J* = 8.55 Hz, 2H), 7.36-7.34 (m, 2H), 3.82 (s, 3H), 2.39 (t, *J* = 7.22 Hz, 2H), 1.33-1.29 (m, 2H), 0.68 (t, *J* = 7.50 Hz, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 192.2, 180.9, 167.3, 165.1, 141.0, 138.1, 136.2, 135.7, 135.6, 132.3, 131.8, 131.2, 130.5, 129.6, 129.4, 129.1, 127.7, 126.8, 52.5, 38.6, 22.8, 12.8; **HRMS** (EI-TOF): calcd for $C_{30}H_{22}ClNNaO_5S$ $[M+Na]^+$: 566.0799, found: 566.0799.

*4.3. General procedure for the synthesis of compounds **7**.*

Following the same procedure for the synthesis of **4**, β-ketothioamide **6** (0.5 mmol) was added instead of *N,S*-acetal. The reaction mixture was heated at 100 °C till the completion of reaction (monitored by TLC). The reaction mixture was allowed to cool at room temperature followed by work up using ethyl acetate. The organic layer was dried over anhydrous Na_2SO_4, and solvent was evaporated under reduced pressure. The crude residue thus obtained was purified by column chromatography over silica gel (100-200 mesh) using hexane/ethyl acetate (17:3) as eluent to afford the pure desired products **7** (R_f = 0.50; hexane/ethyl acetate = 70/30).

*4.3.1. 1-Benzoyl-2-(phenylamino)naphtho[2,1-b]thiophene-4,5-dione (**7aa**)*

A brown solid (161.3 mg, 76% yield), Rf = 0.40 (hexane/ethyl acetate = 7:3). Mp: 116-118 °C. **^{1}H NMR** (500 MHz, $CDCl_3$): δ 10.47 (br, 1H), 7.98 (d, *J* = 7.30 Hz, 1H), 7.76 (d, *J* = 6.60 Hz, 2H), 7.46-7.41 (m, 5H), 7.33-7.27 (m, 3H), 7.19 (t, *J* = 7.20 Hz, 1H), 6.99 (t, *J* = 7.22 Hz, 1H), 6.83 (d, *J* = 7.55 Hz, 1H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 192.9, 181.3, 171.4, 166.4, 146.9, 133.4, 133.2, 130.1, 129.9, 129.8, 129.3, 128.7, 126.4, 121.2, 120.8, 115.4; **HRMS** (EI-TOF): calcd for $C_{25}H_{15}NNaO_3S$ $[M+Na]^+$: 432.0665, found: 432.0611.

*4.3.2. 1-(4-Methylbenzoyl)-2-(phenylamino)naphtho[2,1-b]thiophene-4,5-dione (**7ab**)*

A brown solid (171.0 mg, 80% yield), Rf = 0.40 (hexane/ethyl acetate = 7:3). Mp: 131-133 °C. **^{1}H NMR** (500 MHz, $CDCl_3$): δ 10.26 (br, 1H), 7.99 (d, *J* = 7.55 Hz, 1H), 7.68 (d, *J* = 6.90 Hz, 2H), 7.47-7.39 (m, 4H), 7.27-7.19 (m, 2H), 7.12 (d, *J* = 7.75 Hz, 2H), 7.05-7.02 (m, 1H), 6.72 (d, *J* = 7.80 Hz, 1H), 2.33 (s, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 192.7, 181.5, 171.4, 166.0, 146.7, 144.7, 138.7, 136.1, 133.4, 132.0, 131.1, 130.1, 130.0, 129.9, 129.5, 129.4, 126.3, 121.1, 121.0, 120.8, 115.8, 21.8; **HRMS** (EI-TOF): calcd for $C_{26}H_{17}NNaO_3S$ $[M+Na]^+$: 446.0821, found: 446.0767.

*4.3.3. 1-(4-Methoxybenzoyl)-2-(phenylamino)naphtho[2,1-b]thiophene-4,5-dione (**7ac**)*

A brown solid (180.9 mg, 84% yield), Rf = 0.40 (hexane/ethyl acetate = 7:3). Mp: 109-111°C. **^{1}H NMR** (500 MHz, $CDCl_3$): δ 10.08 (br, 1H), 8.01 (d, *J* = 7.50 Hz, 1H), 7.28 (s, 1H), 7.46-7.43 (m, 5H), 7.25-7.21 (m, 2H), 7.08 (t, *J* = 7.52 Hz, 1H), 6.94 (d, *J* = 7.75 Hz, 1H), 6.80 (d, *J* = 7.10 Hz, 2H), 3.80 (s, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 191.6, 181.5, 171.3, 165.6, 164.1, 146.5, 138.7, 133.6, 130.1, 130.0, 129.8, 129.4, 126.2, 121.0, 116.1, 114.1, 55.6; **HRMS** (EI-TOF): calcd for $C_{26}H_{18}NO_4S$ $[M+H]^+$: 440.0951, found: 440.0894.

*4.3.4. 2-(Phenylamino)-1-(4-(trifluoromethylbenzoyl)naphtho[2,1-b]thiophene-4,5-dione (**7ad**)*

A brown solid (170.4 mg, 72% yield), Rf = 0.40 (hexane/ethyl acetate = 7:3). Mp: 155-157 °C. **^{1}H NMR** (500 MHz, $CDCl_3$): δ 10.65 (br, 1H), 8.00 (d, *J* = 7.55 Hz, 1H), 7.87 (d, *J* = 7.65 Hz, 2H), 7.57 (d, *J* = 7.90 Hz, 2H), 7.50-7.47 (m, 2H), 7.44-7.43 (m, 2H), 7.31 (t, *J* = 7.22 Hz, 1H), 7.22 (t, *J* = 7.50 Hz, 1H), 7.00 (t, *J* = 7.57 Hz, 1H), 6.57 (d, *J* = 7.75 Hz, 1H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 191.4, 181.1, 171.5, 167.4, 146.7, 142.0, 138.4, 133.2, 130.3, 130.2, 130.1, 129.9, 129.7, 126.9, 121.5, 114.5; **HRMS** (EI-TOF): calcd for $C_{26}H_{14}F_3NNaO_3S$ $[M+Na]^+$: 500.0539, found: 500.0473.

*4.3.5. 1-(Furan-2-carbonyl)-2-(phenylamino)naphtho[2,1-b]thiophene-4,5-dione (**7ae**)*

A brown solid (140.2 mg, 71% yield), Rf = 0.40 (hexane/ethyl acetate = 7:3). Mp: 223-225 °C. **^{1}H NMR** (500 MHz, $CDCl_3$): δ 10.25 (br, 1H), 7.99 (d, *J* = 7.55 Hz, 1H), 7.39 (t, *J* = 7.57 Hz, 2H), 7.33 (d, *J* = 7.80 Hz, 2H), 7.26-7.19 (m, 4H) 7.14 (t, *J* = 7.65 Hz, 1H), 6.95 (d, *J* = 7.75 Hz, 1H), 6.42 (s, 1H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 181.55, 179.15, 171.49, 166.38, 146.89, 138.62, 134.01, 131.14, 130.17, 129.34, 126.56, 121.27, 113.24; **HRMS** (EI-TOF): calcd for $C_{23}H_{14}NO_4S$ $[M+H]^+$: 400.0638, found: 400.0635.

*4.3.6. 2-(Phenylamino)-1-(thiophene-2-carbonyl)naphtho[2,1-b]thiophene-4,5-dione (**7af**)*

A brown solid (151.5 mg, 74% yield), Rf = 0.40 (hexane/ethyl acetate = 7:3). Mp: 135-137 °C. **^{1}H NMR** (500 MHz, $CDCl_3$): δ 9.82 (br, 1H), 7.96 (d, *J* = 7.6 Hz, 1H), 7.58 (d, *J* = 4.85 Hz, 1H), 7.39-7.30 (m, 5H), 7.22-7.17 (m, 2H) 7.11 (t, *J* = 7.57 Hz, 1H), 7.30 (d, *J* = 7.90 Hz, 1H), 6.84 (t, *J* = 4.32 Hz, 1H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 184.41, 181.40, 171.28, 165.42, 145.99, 144.32, 138.63, 135.78, 135.40, 133.67, 132.21, 131.27, 130.15, 130.12, 129.62, 129.57, 129.34, 128.48, 126.43, 121.31, 121.08, 116.02; **HRMS** (EI-TOF): calcd for $C_{23}H_{14}NO_3S_2$ $[M+H]^+$: 416.0410, found: 416.0410.

*4.4. General procedure for the synthesis of compounds **9**.*

In an oven dried 25 mL round bottom flask, 0.5 mmol of compound **4**, 0.5 mmol of 1,2-diaminobenzene **8** and 10 mol % of L-Proline were taken. The reaction mixture was heated at 100 ^oC under solvent-free conditions till the completion of the reaction (monitored by TLC). The residue thus obtained was recrystallized with dichloromethane (DCM) to give the pure desired product **9**.

*4.4.1. (2-(Methylthio)-1-phenyl-1H-benzo[a]pyrrolo[3,2-c]phenazin-3-yl)(p-tolyl)methanone (**9aba**)*

A yellow solid (241.0 mg, 96% yield), Rf = 0.40 (hexane/ethyl acetate = 7:3). Mp: 228-230 °C. **^{1}H NMR** (500 MHz, $CDCl_3$): δ 9.36 (d, *J* = 7.95 Hz, 1H), 8.22 (d, *J* = 9.80 Hz, 1H), 8.02 (d, *J* = 7.75 Hz, 2H), 7.83 (d, *J* = 7.90 Hz, 1H), 7.73-7.70 (m, 1H), 7.65-746 (m, 9H), 7.29 (d, *J* = 7.95 Hz, 2H), 2.42 (s, 3H), 2.09 (s, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 195.5, 144.8, 142.3, 140.8, 140.3, 139.5, 136.2, 135.9, 132.4, 130.3, 130.1, 129.5, 129.4, 129.3, 129.3, 129.1, 129.0, 128.9, 128.6, 126.4, 125.7, 125.6, 124.4, 122.6, 21.84, 20.8; **HRMS** (EI-TOF): calcd for $C_{34}H_{24}N_3OS$ $[M+H]^+$: 510.1635, found: 510.1635.

*4.4.2. (11-Chloro-2-(methylthio)-1-phenyl-1H-benzo[a]pyrrolo[3,2-c]phenazin-3-yl)(2-methoxyphenyl)methanone (**9acb**)*

A yellow solid (261.3 mg, 92% yield), Rf = 0.40 (hexane/ethyl acetate = 7:3). Mp: 204-206 °C. **^{1}H NMR** (500 MHz, $CDCl_3$): δ 9.32 (d, *J* = 8.35 Hz, 1H), 8.22-8.12 (m, 2H), 7.85 (d, *J* = 7.50 Hz, 1H), 7.66-7.58 (m, 6H), 7.54-7.50 (m, 1H), 7.45-7.38 (m, 3H), 7.02-7.00 (m, 2H), 3.77 (s, 3H), 2.00 (s, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 194.7, 159.6, 140.9, 140.4, 139.5, 138.7, 134.3, 132.4, 130.6, 130.4, 130.4, 130.3, 130.2, 129.9, 129.2, 129.2, 128.7, 128.6, 128.6, 128.3, 128.0, 127.5, 126.4, 126.2, 125.9, 124.8, 120.4, 112.2, 55.9, 20.4; **HRMS** (EI-TOF): calcd for $C_{33}H_{23}ClN_3O_2S$ $[M+H]^+$: 560.1194, found: 560.1200.

*4.4.3. [1,1'-Biphenyl]-4-yl(2-(methylthio)-1-phenyl-1H-benzo[a]pyrrolo[3,2-c]phenazin-3-yl)methanone (**9aja**)*

A yellow solid (260.1 mg, 90% yield), Rf = 0.40 (hexane/ethyl acetate = 7:3). Mp: 241-243 °C. **^{1}H NMR** (500 MHz, $CDCl_3$): δ 9.38 (d, *J* = 8.90 Hz, 1H), 8.25 (d, *J* = 8.55 Hz, 1H), 8.19 (d, *J* = 8.40 Hz, 2H), 7.87 (d, *J* = 7.50 Hz, 1H), 7.73-7.72 (m, 3H), 7.68-7.67 (m, 6H), 7.58 (d, *J* = 8.85 Hz, 1H), 7.54 (d, *J* = 7.35 Hz, 3H), 7.50-7.45 (m, 3H), 7.41-7.38 (m, 1H), 2.18 (s, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 195.4, 146.4, 142.3, 140.9, 140.4, 139.8, 139.5, 137.1, 136.2, 132.6, 130.7, 130.2, 129.6, 129.4, 129.3, 129.3, 129.1, 128.9, 128.6, 128.3, 127.4, 127.3, 126.4, 125.8, 124.5, 20.9; **HRMS** (EI-TOF): calcd for $C_{38}H_{26}N_3OS$ $[M+H]^+$: 572.1791, found: 572.1803.

*4.4.4. (11-Chloro-2-(ethylthio)-1-phenyl-1H-benzo[a]pyrrolo[3,2-c]phenazin-3-yl)(4-methoxyphenyl)methanone (**9amb**)*

A yellow solid (270.1 mg, 94% yield), Rf = 0.40 (hexane/ethyl acetate = 7:3). Mp: 229-231 °C. **^{1}H NMR** (500 MHz, $CDCl_3$): δ 9.31 (d, *J* = 7.50 Hz, 1H), 8.23-8.15 (m, 1H), 8.02 (d, *J* = 8.40 Hz, 2H), 7.85 (d, *J* = 7.85 Hz, 1H), 7.65-7.52 (m, 6H), 7.48 (d, *J* = 7.45 Hz, 2H), 7.44-7.38 (m, 1H), 6.96 (d, *J* = 8.50 Hz, 2H), 3.87 (s, 3H), 2.51 (q, *J* = 7.31 Hz, 2H), 1.00 (t, *J* = 7.47, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 194.2, 164.2, 161.6, 142.4, 140.9, 139.43, 138.7, 136.7, 135.1, 134.6, 132.5, 131.5, 130.6, 130.4, 130.2, 130.0, 129.4, 129.3, 128.7, 128.6, 128.0, 127.5, 126.5, 126.4, 125.9, 124.6, 114.0, 55.5, 31.4, 14.6; **HRMS** (EI-TOF): calcd for $C_{34}H_{25}ClN_3O_2S$ $[M+H]^+$: 574.1351, found: 574.1358.

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Supplementary Material

Supplementary data (^{1}H and ^{13}C NMR spectra of compounds and X-ray crystallography data for compound **4ak**) associated with this article can be found in the online version, at http://dx.doi.

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