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One-Pot Synthesis of Diverse Collections of Benzoxazepine and Indolopyrazine Fused to Heterocyclic Systems

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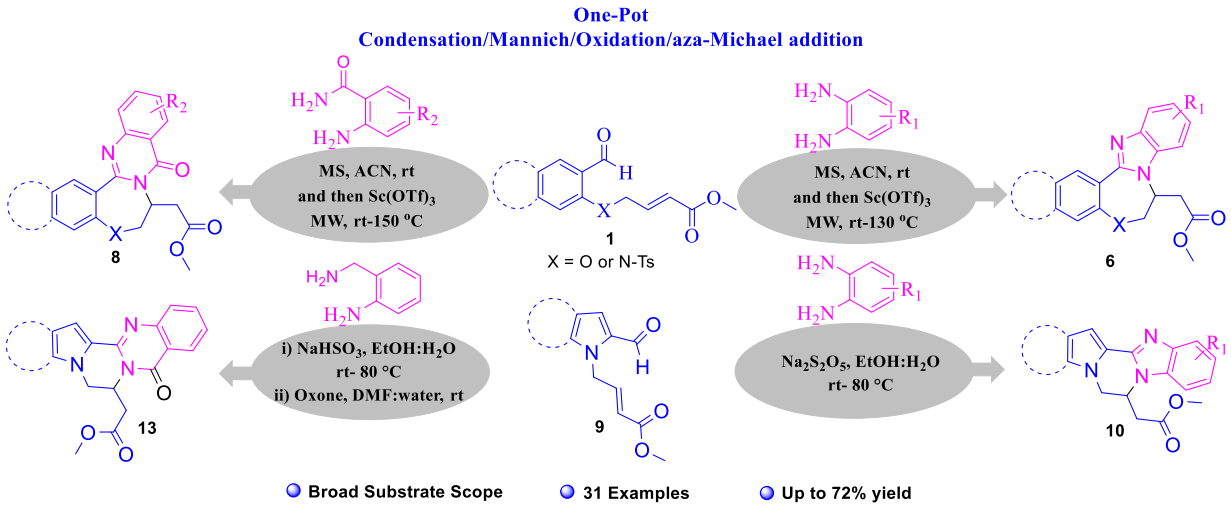


ABSTRACT: The development of efficient and modular synthetic methods for the synthesis of diverse collection of privileged substructures needed for a drug design and discovery campaign, is highly desirable. Benzoxazepine and indolopyrazine ring systems form the core structures of distinct members of biologically significant molecules. Several members of these families have gained attention due to their broad biological activities, which depend on the type of ring-fusion and peripheral substitution patterns. Despite the potential applications of these privileged substructures in drug discovery, efficient, atom-economic and modular strategies for their access

are underdeveloped. Herein, a one-step build/couple/pair strategy that uniquely allows access to diversely functionalized benzoxazepine and indolopyrazine scaffolds, is described. The methodology features a one-pot combination of condensation, Mannich, oxidation and aza-Michael addition reactions, employing a variety of functionalized anilines and aldehydes suitably poised with Micheal acceptor. Scandium triflate ($Sc(OTf)_3$) in acetonitrile (ACN) was found to promote the construction of benzoxazepines scaffolds, while sodium metabisulfite ($Na_2S_2O_5$) in aqueous EtOH rapidly enhanced the cascade reaction that led to diverse collections of indolopyrazine frameworks. These protocols represent modular, efficient and atom-economic access of constrained benzoxazepine and indolopyrazine systems with more than ten points of diversity and large substrate tolerance.

INTRODUCTION

The development of mild and modular synthetic strategies for the construction of diverse collections of privileged heterocycles is paramount in the field of drug design and discovery.[1] Such strategies should be high yielding, eco-friendly, operationally simple, and result in a rapid increase in skeletal and structural diversity using readily available starting materials.[1] For the ideal synthesis of privileged substructures needed in a phenotypic screening campaign, the efficiency of the method is judged not by the number of complex steps involved, but by the use of nontoxic and inexpensive catalysts, being operationally simple and it allows the use of a variety of substrates.[2] Thus, inflexibility of the synthetic methods utilized and long reaction steps constitute a major constraint in a library design.

Among the important structural options are benzoxazepines and indolopyrazines, privileged scaffolds that display a broad spectrum of significant biological activities.[3-7] Imidazo-, indolo- and pyrrolo-fused benzoxazepines and indolopyrazines, constitute a range of anticancer,[8] autoimmune[9] and antibacterial agents.[10] Representative examples of bioactive members of these analogues are shown in Figure 1, and exemplified by the prostaglandin E_2 receptor 2 (EP_2) antagonist **A**,[3] for the treatment of Alzheimer's disease, the receptor interacting protein 1 (RIP1) kinase inhibitor **B**,[5] which has potent anticancer activity, and the retinoic acid-related orphan receptor gamma (RORγt) antagonist **C,** used for autoimmune diseases.[9] Other benzoxazepine analogues include pyrrolo-1,5-benzoxazepines (PBOX)-6 and PBOX-15, represented by structure **D** (Figure 1), have been shown to induce apoptosis in acute lymphoblastic leukemia cells.[4] Furthermore, recent reports indicated their potency as inhibitors of phosphoinositide 3-kinases (PI3Ks) for treatment of several diseases

(Structure **E**, Figure 1).[11a] Additionally, pyrrolo-pyrazine system represented by structure **F** (Figure 1) has been reported to possess a potent antitumor activity.[11b] The pentacyclic indole system **G**, indicated a potent antimicrobial activity.[11c] Moreover, the imidazo-fused pyrazine **H** is known to be active as antimalarial agent.[11d]

Owing to their broad biological significance, the synthesis of fused benzo[*b*,*f*]imidazo- and thiazo[1,2-*d*][1,4]oxazepine systems, has been carried out through various methods.[12] Additionally, the synthesis of heterocycles fused to indolopyrazine scaffolds, is underdeveloped.[13] Representative strategies to access heterocyles-fused to benzoxazepine systems include domino aziridine ring-opening and an isocyanide-insertion reaction,[14a] and ring-opening/aza-Michael addition of activated aziridines.[14b] On the other hand, various methods were utilized for the synthesis of indolo fused pyrazine frameworks. Among others are, the intramolecular dehydrogenative cross-coupling with Cu catalyst,[15a,b] Pd-catalyzed regioselective intramolecular dehydrogenative cross coupling,[15c] Ir-catalyzed asymmetric allylic amination[15d] and photocyclization and photochemical dehydrogenation reactions.[10b]

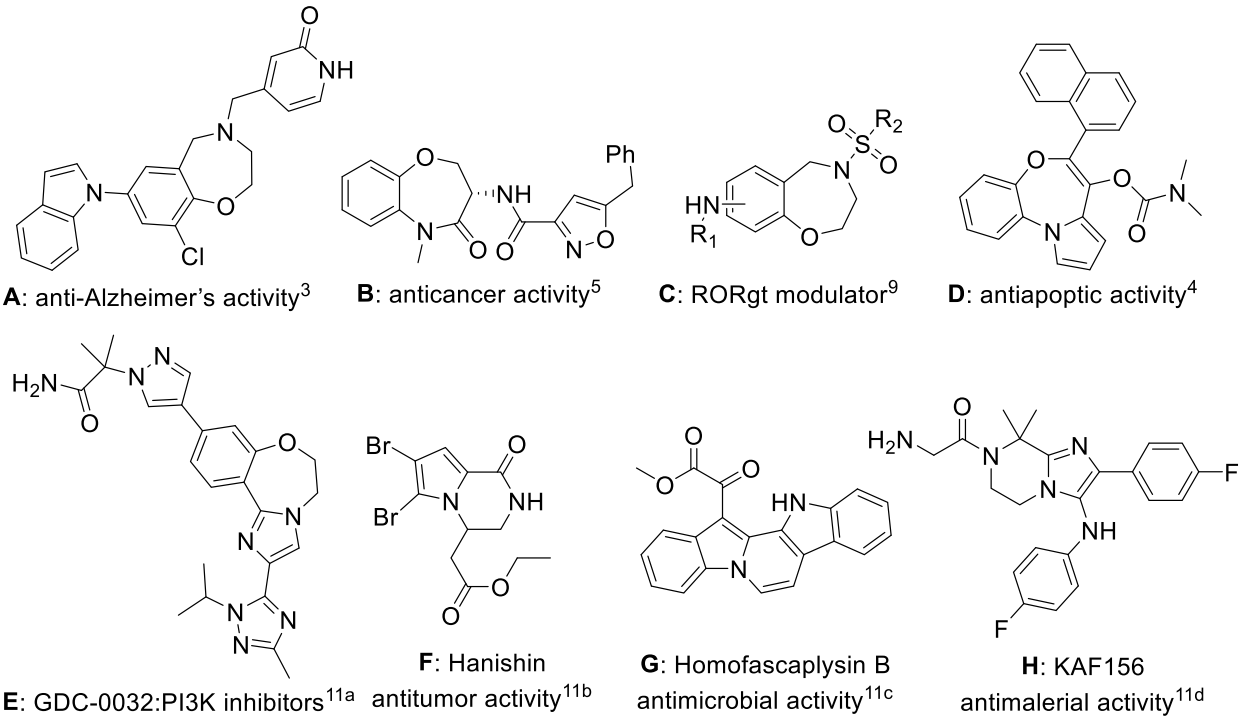
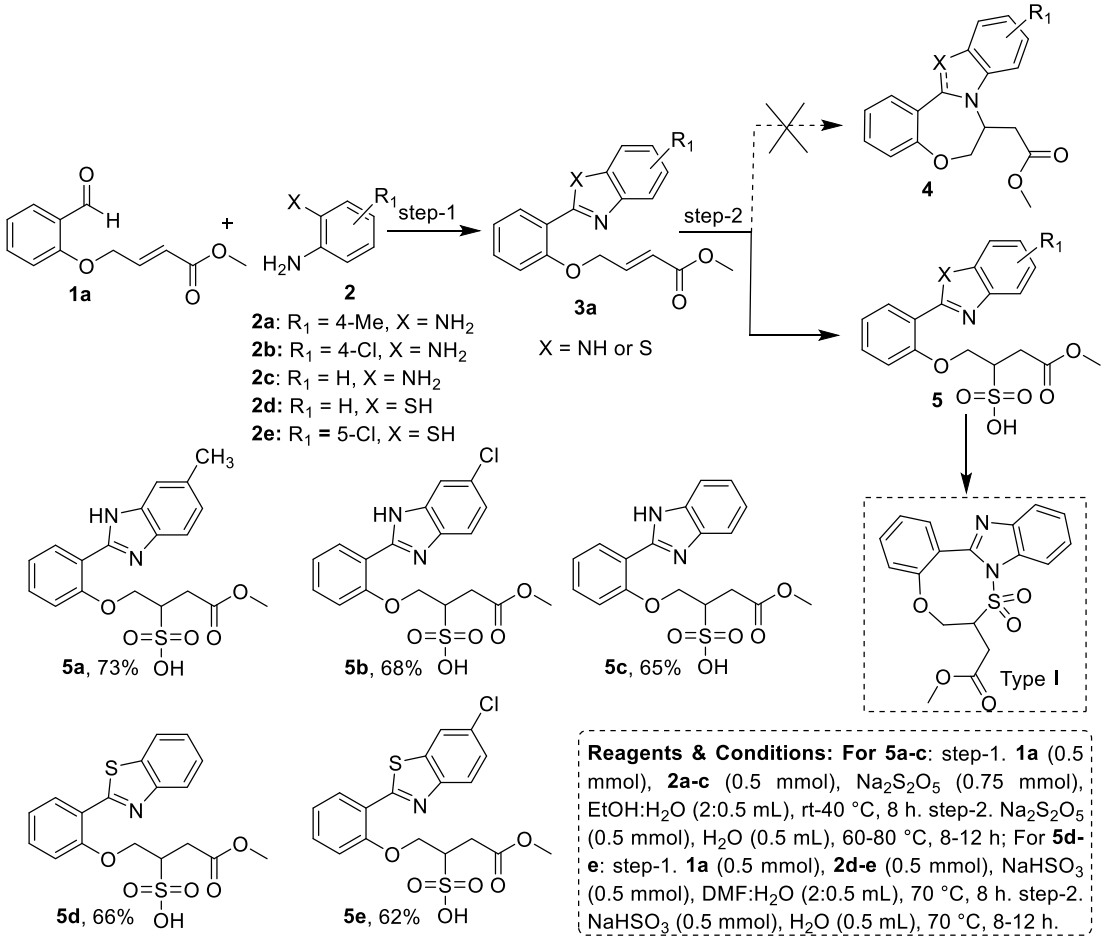


Figure 1. Representative structures of bioactive benzoxazepine and indolopyrazine analogues.

Although these protocols represent important methods for the synthesis of benzoxazepine and indole fused pyrazine systems, many of these strategies utilize multi-step procedures, harsh reaction conditions, toxic catalysts and solvents, preparation of synthetically challenging intermediates, and poor overall yields. Additionally, the peripheral substitution pattern and the type of ring fusion have profound effects on their biological activities (Figure 1).[3-5,9,11a-e] Furthermore, given the conformational flexibility of the 7-membered ring benzoxazepine core, constrained analogues might exhibit diverse biological activities that might be largely affected by the ring-fusion patterns.[3-5,9,11a-b] Therefore, it was believed that the lack of modular and efficient synthetic strategies to rapidly access these scaffolds have restricted systematic studies toward multiple phenotypes. Hence, establishing a modular cascade for the rapid access of these analogues would be a remarkable achievement. In this context, one of the key objectives of this work, is the development of efficient and mild methods to rapidly access diverse collections of scaffolds that represent the basic core of biologically relevant compounds.[16] Thus, an operationally simple protocol for the construction of skeletally diverse benzoxazepine and indolopyrazine scaffolds fused to various classes of heterocylic rings, is accomplished. This design was inspired by a previous experience in the reactivity and applications of the central element **1a** (Scheme 1).[16c-d] Accordingly, it was envisaged that the addition of an aryl diamine-based ambident nucleophile to a binucleophuge, an aldehyde suitably poised with Michael acceptor, should generate benzimidazole and/or benzoquinazoline systems which subsequently initiates the intramolecular aza-Michael addition reaction leading to the tetracyclic benzimidazo- or benzoquinazoline-fused benzoxazepine scaffolds of the types **6a** and **8**, respectively (Schemes 2 and 4). Herein, the successful implementation of this cascade combining condensation/Mannich/oxidation/aza-Michael addition reactions in one-pot, is presented.

Scheme 1. Preparation of 2-arylbenzimdazole/thiazole sulfonic acid derivatives

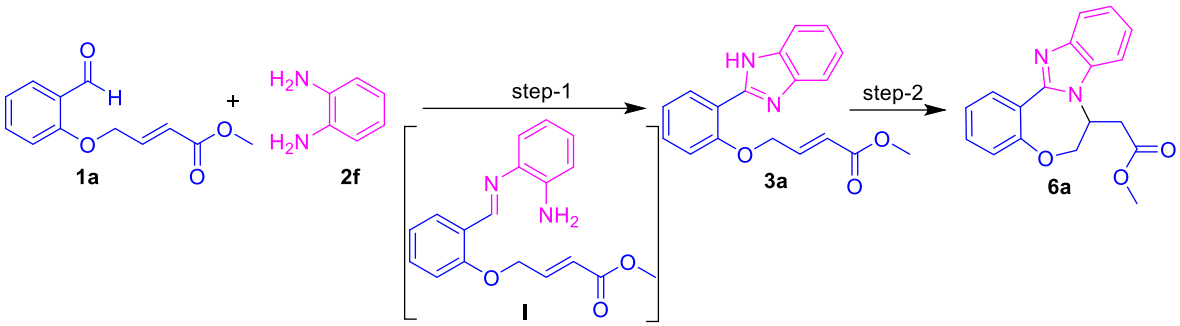


RESULTS AND DISCUSSION

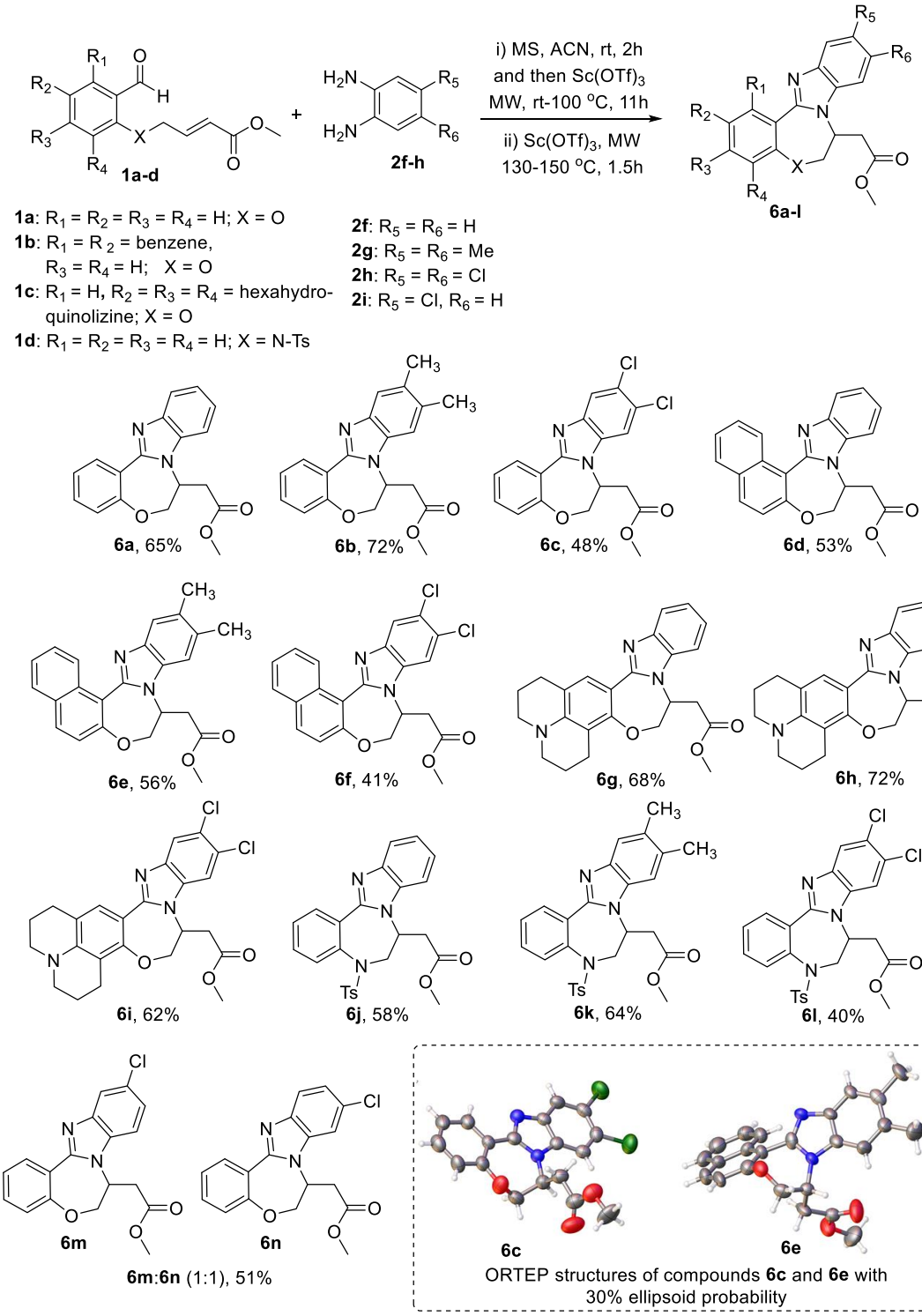
Synthetic Design. The synthetic plan is commenced as described in Scheme 1. For the synthesis of the benzimidazole intermediate **3a**, many conditions have been reported for the construction of similar scaffolds.[17] However, it was anticipated that only a few would be suited for our strategy to provide a general one-step protocol that facilitates the proposed cascade and tolerates a wide range of substrates. Therefore, many relevant reaction parameters were systematically explored. Among the catalysts utilized to promote the synthesis of benzimidazoles is sodium metabisulfite ($Na_2S_2O_5$).[17] Thus, it was found that the use of $Na_2S_2O_5$ in aqueous EtOH rapidly provided the desired benzimidazole intermediate **3a**, which was detected through LCMS analysis. Without purification, treatment of the latter with another 1.0 equivalent of $Na_2S_2O_5$ in EtOH/H_2O at 60 °C, gave rise to a product with a structure that is thought to belong to the desired benzoxazepine **4**. Surprisingly, this product was identified to be the unexpected product **5**. Clearly, the sulfur atom

in the SO_3^{2-} fragment arising from $Na_2S_2O_5$, added to the β-carbon of the Michael adduct in **3a**, leading to **5**. This protocol turns out to be a general procedure for the synthesis of these scaffolds.[18] Thus, employing various phenylene diamines, i.e. **2a-c** and aminothiophenols **2d-e** as starting materials, delivered the corresponding β-sulfonic acid products, **5a-e**. The structures of these compounds were confirmed though high resolution mass spectroscopy (HRMS), 1D- and 2D-NMR analysis (Supporting Information). At this point in time, it was envisioned that these products might be differentiated to complex systems through coupling between the sulfonic acid residue and the NH group of the imidazole ring. Thus, many attempts were made to promote this transformation, if successful; we would have had in hand, an eight-membered ring sulfone amide system of type **I** (Scheme 1). Unfortunately, all attempts using different reagents and conditions (T3P, TBTU, $POCl_3$ and $SOCl_2$), failed to promote the formation of the eight-membered system **I**. At this junction, efforts were directed toward finding the best conditions to promote the Mannich and the aza-Michael addition steps for the construction of systems of type **4** (Scheme 1). Hence, many reaction conditions and catalysts were explored, including $Sc(OTf)_3$, ACOH, and TFA. Unfortunately, none of these conditions were found to be compatible with the cascade reaction. To our delight, it was found that the reaction proceeded smoothly when reacting the phenylenediamine (**2f**) with aldehyde **1a** at rt for 2h in the presence of molecular sieves to produce the imine intermediate **I** (Scheme 2). Subsequent addition of 10 mol% of $Sc(OTf)_3$ was found to affect the formation of intermediate **3a**. Subjecting the latter to another 10 mol% of $Sc(OTf)_3$ under microwave conditions at 130 ^oC, produced the benzimidazo- fused benzoxazole system **6a** in 65% yield. The structure of the latter was unambiguously confirmed through 1D- and 2D-NMR analysis. A salient feature in the ^{13}C NMR spectrum of compound **6a** is the downfield chemical shift of the angular methine carbon which appeared at δ 53.5 ppm (evidenced from its HSQC spectrum, Supporting Information), unambiguously confirming that the imidazolyl sp^3 nitrogen proceeded to the intramolecular aza-Michael addition leading to the benzoxazepine system (Scheme 2).

Scheme 2. One-pot synthesis of imidazole fused benzoxazepines. Step-1: 1a (0.25 mmol), 2a (0.25 mmol), molecular sieves, ACN (2 mL), rt, 2h, and then $Sc(OTf)_3$ (10 mol%), MW, rt-70 °C, 11h. Step-2: $Sc(OTf)_3$ (10 mol%), MW, 130 °C, 1.5 h



Scheme 3. Synthesis of various imidazole fused to benzoxazepine and benzodiazapine scaffolds

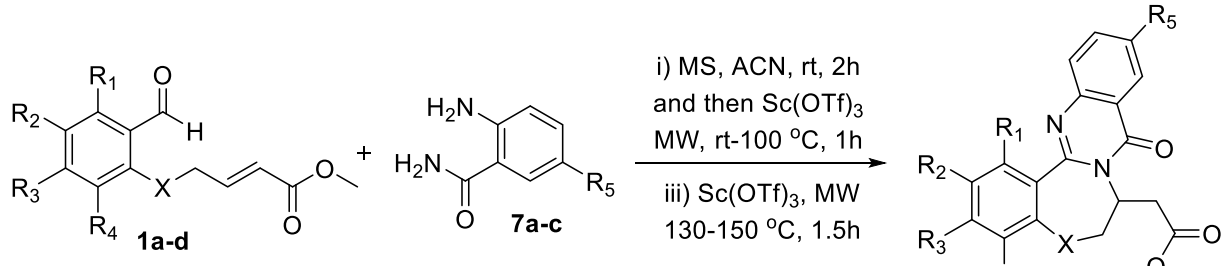


Synthesis of skeletaly diverse benimidazole-fused benzoxazepines. With the optimized conditions in hand, we next investigated the substrate scope of the cascade using the aldehyde **1a**

and various anilines **2f-h**, to yield the corresponding tetracyclic benzimidazole-fused benzoxazepine systems in fairly good overall yields (**6a-c**, Scheme 3). Notably, electron-withdrawing or -donating moieties on the aromatic amines had no significant impact on the overall yields (Scheme 3). To unambiuously confirm the structures of these systems, the structure of **6c** was confirmed through X-ray crystaloghraphic analysis (Scheme 3 and Table S1). To further extend the scope of this cascade, naphthylaldehyde **1b**, was found to be equally suited for the tandem process, producing compounds **6d-f** in fairly good yields. The structure of **6e** was confirmed through X-ray crystaloghraphic analysis (Scheme 3 and Table S2).

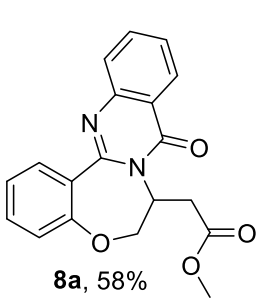
To increase the skeletal diversity of the pilot library, a quinolizine-fused aldehyde **1c** was proposed as a substrate. While its reaction proceeded slowly (**6g-i**) the overall isolated yields were relatively high compared to bicyclic aromatic aldehydes. With the robust reaction conditions in hand, it was envisaged to widen the scope of the cascade to produce skeletally diverse polycyclic scaffolds. Thus, the use of N-Ts-substituted aldehyde, **1d**, was considered and found to be suitable with the cascade conditions to deliver the benzoimidazo-fused benzodiazepine systems **6j-l**, in fairly good yields. The latter represents the core scaffold of many biologically significant compounds, that include anticonvulsant, antipsychotics, muscle relaxant and antimicrobial agents.[19] To test the regiochemistry of the reaction, mono substituted phenylene diamine was introduced as one of the reaction components. As expected, the reaction of 4-chloro phenelynediamine (**2i**) under the obtimized reaction conditions, deilvered a 1:1 mixture of regioisomers (**6m** and **6n**) as concluded from its ^{1}H and ^{13}C NMR spectra (Scheme 3 and Supporting Information).

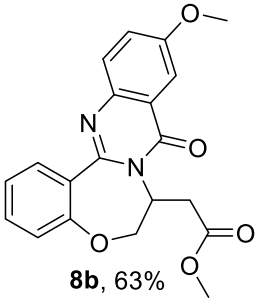
Scheme 4. Synthesis of various quinazoline fused to benzoxazepine and benzodiazapine derivatives

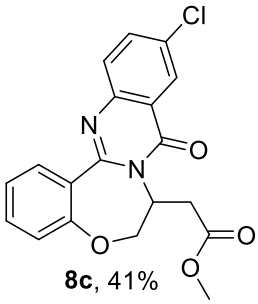


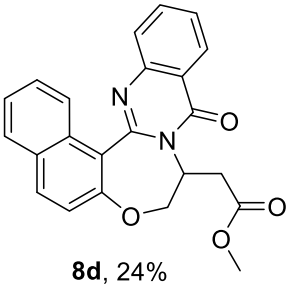
1a: $R_1 = R_2 = R_3 = R_4 = H$; X = O
1b: $R_1 = R_2$ = benzene, $R_3 = R_4 = H$; X = O
1c: $R_1 = H$, $R_2 = R_3 = R_4$ = hexahydro-quinolizine; X = O
1d: $R_1 = R_2 = R_3 = R_4 = H$; X = N-Ts

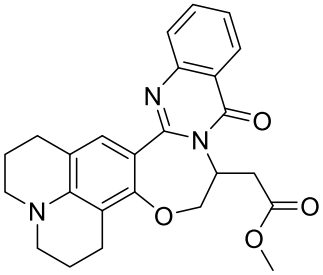
7a: $R_5 = H$
7b: R_5 = OMe
7c: R_5 = Cl

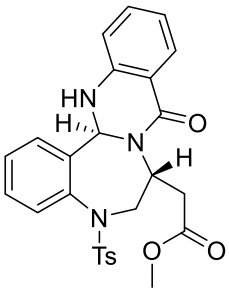

8a, 58%

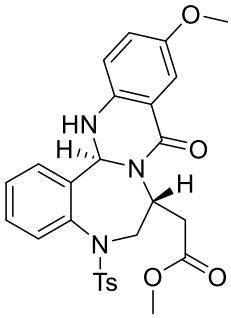

8b, 63%

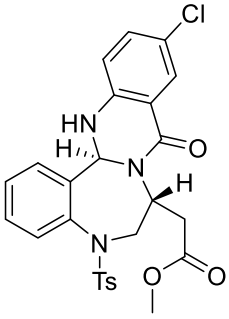

8c, 41%

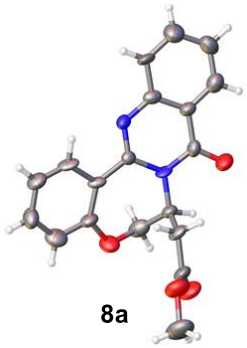

8d, 24%

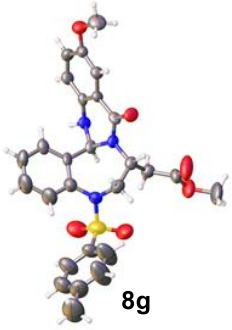

8e, 52%


8f, 54%, >99% dr


8g, 58%, >99% dr


8h, 48%, >99% dr

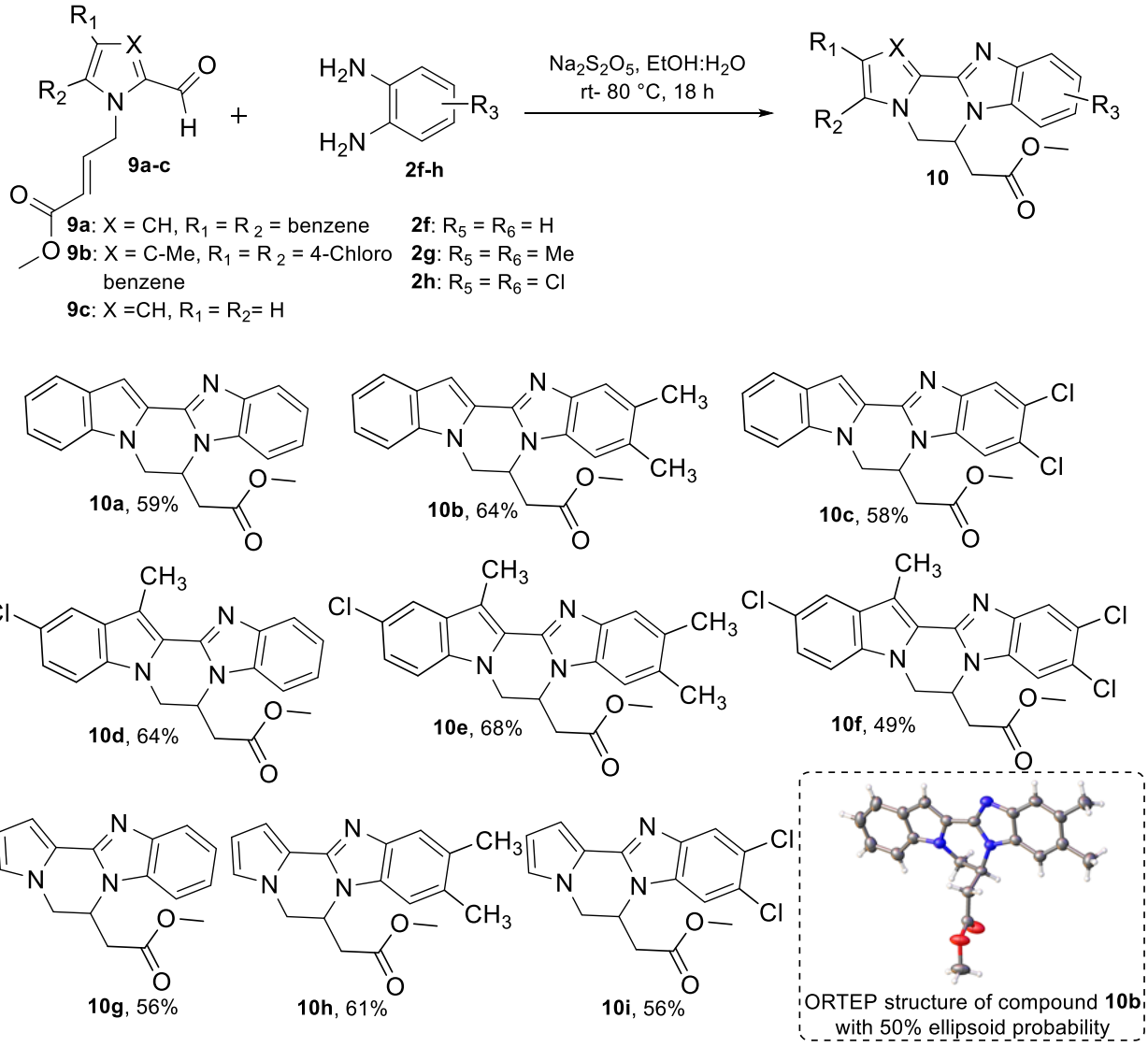

8a


8g

ORTEP structures of compounds **8a** and **8g** with 40% and 30% ellipsoid probability, respectively

Synthesis of quinazolinone-fused benzodiazepines. In addition to the structural diversity of the anilines and aldehydes used thus far, a second diversity element was incorporated into the library design by employing aminobenzamides as ambident nucleophiles. Hence, it was envisioned that applying the same chemistry to the 2-aminobenzamide systems **7a-c** (Scheme 4), would allow for additional skeletal diversity within the pilot library. To demonstrate this, the 2-aminobenzamides **7a-c** were reacted with aldehyde **1a** under the optimized reaction conditions to furnish the corresponding quinazolinone fused to benzoxazepine systems **8a-c** in good overall yields. A Salient feature of the ^{13}C-NMR spectrum of compound **8a**, is the cyclic methine carbon resonating at δ 49.3 ppm, providing a concrete evidence for the formation of the benzoxazepine ring, which was further confirmed by X-ray crystallographic analysis (Scheme 4 and Table S3). The skeletal diversity of the quinazoline products arising from the aminobenzamide ambident nucleophile, was expanded to include the polycyclic systems **8d** and **8e**. To further diversify this pilot library, the NTs-tethered aldehyde **1d** was introduced in the cascade as a starting material, to deliver diastereoselectively the quinazolinone fused to benzodiazepine systems **8f-h**. Surprisingly, the oxidation reaction leading to the double bond formation similar to **8a-8e** systems, was found to be incompatible with this scaffold, despite the many attempts to variate the reaction conditions. To unambiguously confirm the delicate stereochemistry around these systems, NOSEY studies did not indicate reciprocal interactions between the methine protons resident on the chiral carbons, confirming their trans-disposition (Supporting Information). An X-ray analysis was carried out for compound **8g** (Scheme 4 and Table S4) to unequivocally confirm the preceding NOSEY results.

Scheme 5. Synthesis of imidazole fused to pyrrolo- and indolo-pyrazine systems

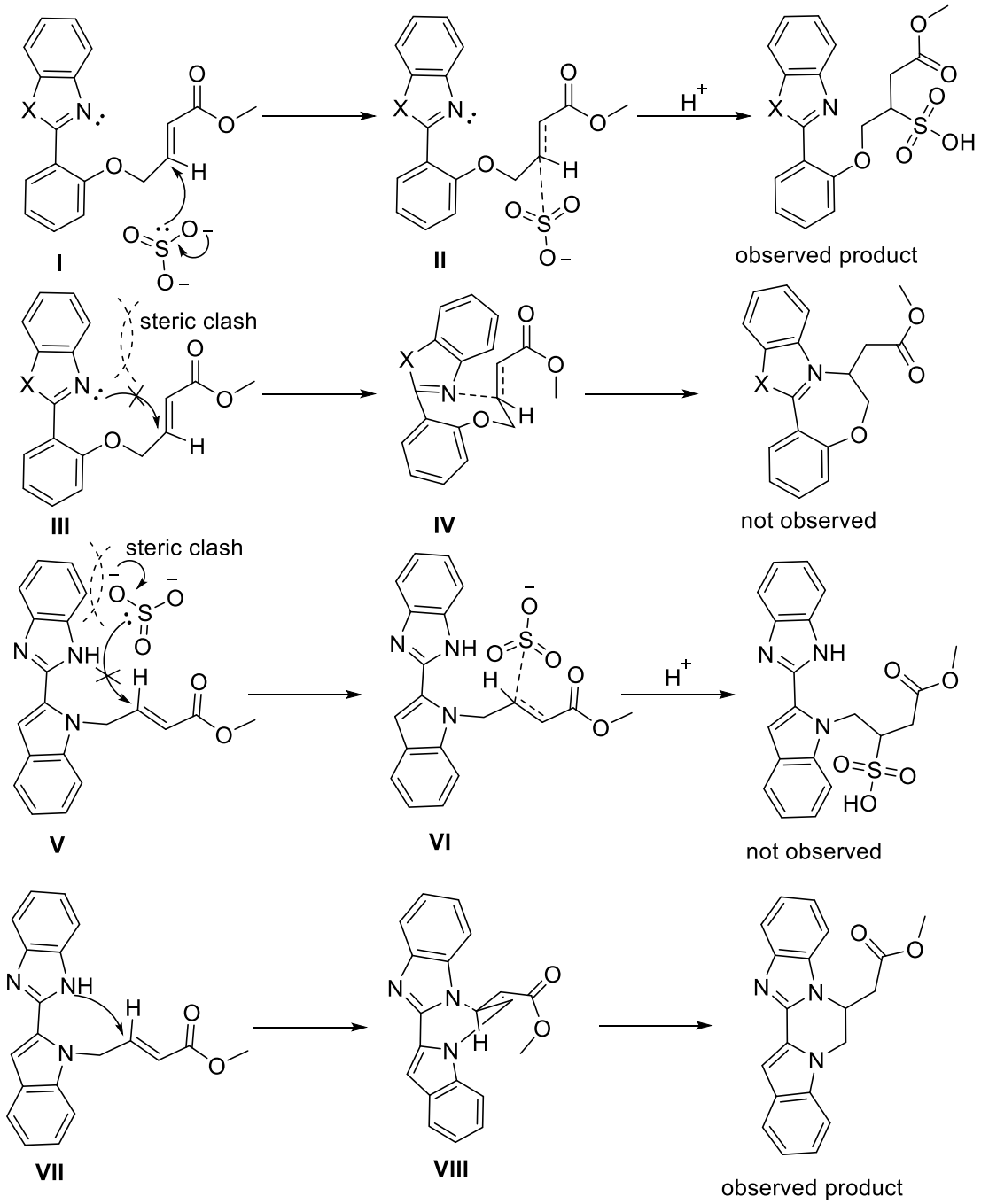


Synthesis of indolo- and pyrrolo-benzimidazopyrazine scaffolds. In order to expand the scaffold diversity in the pilot compound library, it was decided to incorporate a second ring-size diversity element in the synthetic design. Thus, it was believed that this could be achieved through the reaction between the aldehyde **9a** and the phenylene diamine (**2f**). If successful, we would have had in hand a complex ring system that encompasses an indole fused to benzimidazopyrazine framework of type **10**. The latter, represents the basic core of many biologically important molecules including anticancer and antibacterial motifs.[11d,20] To test the validity of this plan, a solution of $Na_2S_2O_5$ in aqueous ethanol was utilized as a possible promoter of the proposed cascade

reaction, Scheme 1 (*vide supra*). Interestingly, it was found that the use of $Na_2S_2O_5$ in aqueous EtOH at 25 to 80 °C for 12h, is compatible with this cascade and gave rise to the desired product dihydrobenzo[4',5']imidazo[2',1':3,4]- pyrazino[1,2-*a*]indol **10**. Thus, reaction of indolyl aldehyde **9a** with phenylene diamine **2f**, under the optimized reaction conditions, furnished the tetrahydropyrazino[1,2-*a*]indole system **10a**. The structure of **10a**, was unambiguously confirmed by extensive 1D- and 2D-NMR studies. A salient feature of the ^{13}C NMR spectrum of **10a**, is the chemical shift of the cyclic methine carbon resonating at δ 48.7 ppm, which was also concluded from the correlations in its HSQC-2D spectrum (Supporting Information).

To explain this controversial reactivity of aldehydes **1a** and **9a** with phenylene diamine under $Na_2S_2O_5$ in EtOH/H_2O conditions, one should consider the steric bias that dictates the products produced by the two reactions. Obviously, under these conditions, the formation of a six-membered indolo-tetrahydopyrazine scaffold **10a**, through intramolecular aza-Michael addition (intermediate **VII**, Scheme 6), is rather more preferred than the nucleophilic Michael addition of the SO_3^{2-} group due the steric compression imposed by the indolyl group (intermediate **V**, Scheme 6). However, the nucleophilic Michael addition of the SO_3^{2-} group on intermediate **I** dominates, since the aryloxy arm is relatively away from the β-carbon (intermediate **II**, Scheme 6). Therefore, the steric compression between the aryloxy and the benzimidazole groups, hinders the attack of the benzimidazole NH group on the α,β-unsaturated ester. In another aspect, the aza-Michael addition in intermediate **III** might be deviated from the right angle needed to form **IV**, when compared to that in intermediate **VII** leading to **VIII**. Besides, the formation of a six membered-ring system is rather thermodynamically more preferred than a seven-membered ring analogue.

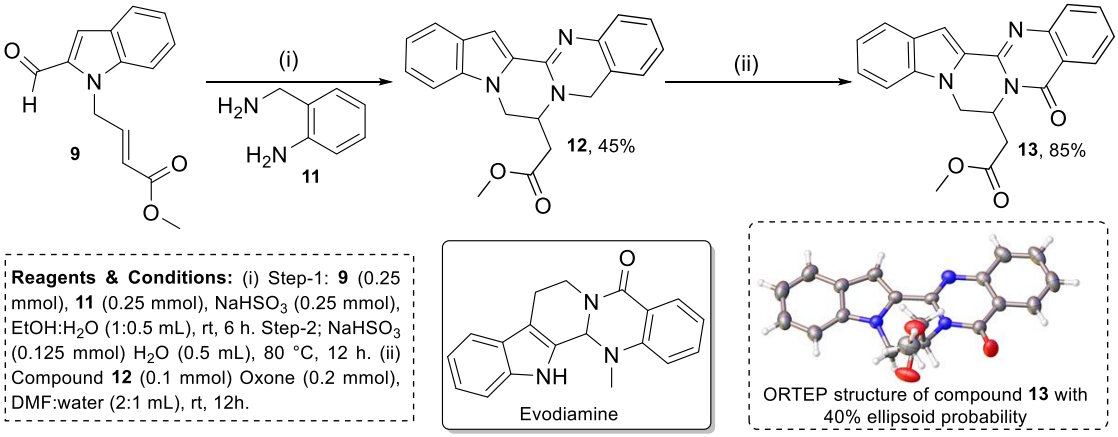
Scheme 6. Rational for the formation of the sulfonic acid and pyrazine products using sodium metabisulfite



With the optimized conditions in hand, the attention is directed towards the synthesis of a pilot library of these polycyclic tetrahydropyrazine systems. Thus, reactions between aldehydes **9a-b** and phenylene diamines **2f-h**, delivered the polysubstituted indolo-tetrahydropyazine systems **10b-f** in fairly good yields. To unambiguously confirm the structures of these systems, compound

10b was chosen as a representative model for X-ray crystallographic analysis (Scheme 5 and Table S5). To further diversify the library, a ring-based diversity element was introduced when the pyrolyl aldehyde **9c** was used as a nucleophuge. Thus, reaction of **9c** with various substituted phenylene diamines delivered the pyrrolo-fused tetrahydropyrazine systems **10g-i** in relatively fair yields. To broaden the skeletal diversity of the tetrahydropyrazino[1,2-*a*]indole scaffolds, the indolyl aldehyde binucleophuge **9** was subjected to reaction with the ambident nucleophile 2-aminobenzylamine (**11**) to deliver the indolo-fused pyrazino[1,2-a]quinazoline **12** in satisfactory yield (Scheme 7). The latter represents the basic core of evodiamine, a natural product isolated from *Evodiae fructus*.[21a-d] Evodiamine has been included in some dietary preparations as it has been shown to reduce fat uptake in animals.[21e] Recently, it has also been reported that evodiamine possesses anticancer activity by inhibition of the human DNA topoisomerase I.[21f] Interestingly, stirring compound **12** in the presence of oxone in DMF:water delivered the oxidized product **13** in a quantitative yield. The structure of which was unambiguously confirmed from its NMR spectra and X-ray crystallographic analysis (Scheme 7 and Table S6). The absence of the quinazoline methylene carbon of **12** in its ^{13}C NMR spectrum, was reflected by the amide carbon resonating at 161 ppm. Further confirmation of the structure was concluded from the 2D-NMR connectivities (HSQC and HMBC, Supporting Information). To further elaborate on the importance of these systems, a 3D-overlay of compounds **10a**, **13** and evodiamine (Figure 2) indicated *ca*. 79% similarity when comparing their 3D-shapes. This rationale indicates the value of our approach toward the synthesis of biologically relevant molecules. In this respect, the flexibility in the choice of the starting materials and the presence of the ester arm in the final products, allow for the synthesis of a diverse library similar to that of evodiamine, hence facilitating comprehensive SAR studies.

Scheme 7. Synthesis of quinazoline fused to indolo pyrazine systems



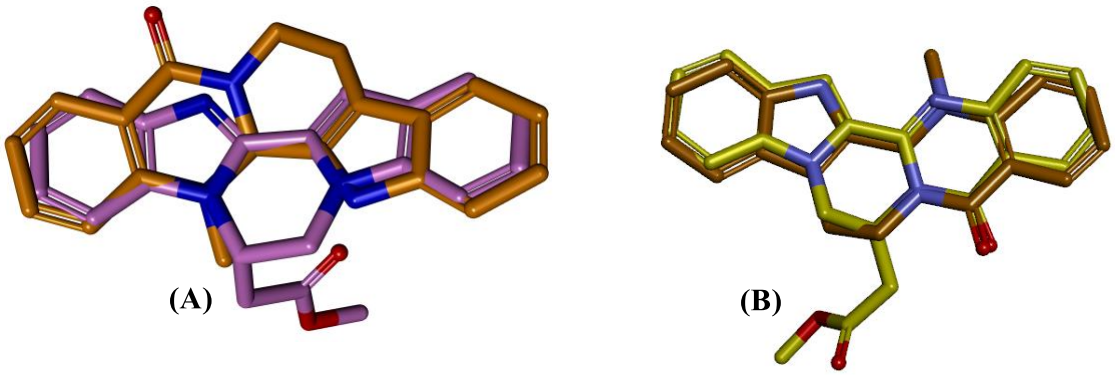


Figure 2 (A). An overlay of evodiamine (brown) and compound **10a** (purple), similarity = 72.6%. **(B)** An overlay of evodiamine (brown) and compound **13** (magenta), similarity = 79.1%.

CONCLUSION

In summary, the work presented in this article, represents a tandem one-pot route to access diverse collections of benzoxazepine and indolopyrazine fused to various heterocylic systems. The catalysts, $Sc(OTf)_3$ or aqueous solution of $Na_2S_2O_5$, were found to mediate the Mannich/aza-Michael addition-cyclization reactions. The use of this approach allowed for the access of a range of complex molecular scaffolds, employing reagent and starting material-based reaction schemes. This concept was validated by the construction of a 31-membered library with a broad distribution of molecular shapes, starting from readily accessible building blocks. The combination of reagent- and starting material-based approaches for the generation of molecular diversity, delivered many important possibilities not achievable by either

method alone. Work is under way in our laboratories to further explore the biological activities of the compound collections.

EXPERIMENTAL SECTION

General Experimental Methods. Chemical reagents and anhydrous solvents were purchased from Sigma-Aldrich and were used without further purification. Solvents for extraction and column chromatography were distilled prior to use. TLC analysis were performed with silica gel plates (0.25 mm, E. Merck, 60 F_{254}) using iodine and a UV lamp for visualization. ^{1}H and ^{13}C NMR experiments were performed on a 500 MHz instrument, respectively. Chemical shifts are reported in parts per million (ppm) downstream from the internal tetramethylsilane standard. Spin multiplicities are described as s (singlet), bs (broad singlet), d (doublet), dd (doubledoublet), td (tripledoublet), t (triplet), q (quartet), or m (multiplet). Coupling constants are reported in Hertz (Hz). ESI mass spectrometry was performed on a Q-TOF high resolution mass spectrometer or Q-TOF Ultim LC-MS. MW irradiation reactions were performed in a selaed vial on CEM synergy microwave synthesizer (version; DSCA02.22). The surface temperaute of the reaction vessel was monitered by IR extrenal surface sensor. Single-crystal X-ray diffraction data were collected using an Oxford Diffraction XCalibur, equipped with (Mo) X-ray Source ($\lambda = 0.71073$ Å) at 293(2) K.

Methyl (*E*)-4-(2-formylphenoxy)but-2-enoate (1a).[16c] NaH (6 mmol) at 0 °C was added to a solution of salicylaldehyde (5 mmol) in DMF (10 mL). After 30 min, a solution of methyl *trans*-4-bromo-2-butenoate (7.0 mmol) in DMF (5 mL) was added dropwise and stirring was continued at rt for 3h. After completion, reaction mixture was quenched with saturated NH_4Cl solution, diluted with ethylacetate (100 mL) and washed with cold water (2 x 50 mL). The organic layer was separated, dried over Na_2SO_4 and concentrated under vacuum. The crude was purified on flash chromatography, using 25% EtOAc in hexane as an eluent to produce the title compound **1a**. White solid (1.1g, 85% yield); ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.56 (s, 1H), 7.90 – 7.86 (m, 1H), 7.63 – 7.50 (m, 1H), 7.20 – 7.06 (m, 2H), 6.96 (d, J = 8.4 Hz, 1H), 6.31 – 6.18 (m, 1H), 4.87 – 4.84 (m, 2H), 3.79 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 189.4, 166.3, 160.2, 141.6, 136.0, 129.0, 125.2, 122.2, 121.6, 112.6, 66.9, 51.9. LCMS (ESI): m/z 221 $[M+H]^+$.

Methyl (*E*)-4-(2-(1H-benzo[d]imidazol-2-yl)phenoxy)but-2-enoate (3a). Sodium metabisulfite (0.75 mmol) in H_2O (0.5 mL) was added to a solution of aldehyde (**1a**, 0.5 mmol) in ethanol (2 mL) at rt. After 30 min, diamine (**2**, 0.5 mmol) was added and stirring was continued at rt for 2 h. The reaction mixture was heated to 40 °C for 8 h. After completion, ethanol was completely removed, and the crude reaction mixture was diluted with EtOAc (20 mL) and extracted with water (10 mL). The organic layer was separated, dried over Na_2SO_4 and concentrated under vacuum. The crude was purified on flash chromatography, using 32% EtOAc in hexane as an eluent to produce the title compound **3a** as off white solid (101 mg, 66% yield); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.61 (d, J = 7.5 Hz, 1H), 7.78 – 7.62 (m, 2H), 7.42 (t, J = 7.3 Hz, 1H), 7.36 –

7.25 (m, 2H), 7.25 – 7.15 (m, 2H), 7.01 (d, *J* = 8.2 Hz, 1H), 6.21 (d, *J* = 15.8 Hz, 1H), 5.04 (s, 2H), 3.80 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.0, 155.3, 149.2, 141.5, 131.4, 130.7, 123.0, 122.9, 122.6, 118.0, 112.8, 67.7, 51.9; HRMS (ESI-TOF): m/z calcd for $C_{18}H_{17}N_2O_3$, 309.1239 found 309.1236 $[M+H]^+$.

General reaction procedure for the preparation of compounds 5a-c. Sodium metabisulfite (0.75 mmol) in H_2O (0.5 mL) was added to a solution of aldehyde (**1a**, 0.5 mmol) in ethanol (2 mL) at rt. After 30 min, diamine (**2**, 0.5 mmol) was added and stirring was continued at rt for 2 h. The reaction mixture was heated to 40 °C for 8 h. After completion of step-1, another one equivalent of sodium metabisulfite (0.5 mmol) in water (0.5 mL) was added and the reaction was heated to 60-80 °C for 8-12 h. After completion, ethanol was completely removed, and the crude reaction mixture was diluted with EtOAc (20 mL) and extracted with water (10 mL). The aqueous layer was concentrated to minimum. Crystallization of the crude mixture from water produced a pure product.

4-Methoxy-1-(2-(6-methyl-1H-benzo[d]imidazol-2-yl)phenoxy)-4-oxobutane-2-sulfonic acid (5a). White amorphous solid (147 mg, 73% yield); ^{1}H NMR (500 MHz, CD_3OD+$CDCl_3$) δ 8.00 (d, *J* = 7.1 Hz, 1H), 7.64 (t, *J* = 6.5 Hz, 2H), 7.60 – 7.55 (m, 1H), 7.31 (d, *J* = 8.4 Hz, 1H), 7.23 (t, *J* = 7.8 Hz, 2H), 4.75 (dd, *J* = 9.6, 2.4 Hz, 1H), 4.57 (dd, *J* = 9.6, 5.9 Hz, 1H), 3.83 – 3.75 (m, 1H), 3.67 (d, *J* = 6.4 Hz, 3H), 3.24 (dd, *J* = 16.1, 7.6 Hz, 1H), 2.82 (dd, *J* = 16.1, 10.0 Hz, 1H) 2.50 (s, 3H); ^{13}C{^{1}H} NMR (125 MHz, CD_3OD+$CDCl_3$) δ 172.6, 157.5, 145.7, 137.8, 136.0, 132.1, 129.8, 129.5, 128.7, 122.7, 114.0, 113.9, 113.5, 111.5, 68.5, 55.9, 52.4, 32.5, 21.8; HRMS (ESI-TOF): m/z calcd for $C_{19}H_{21}N_2O_6S$, 405.1120 found 405.1120 $[M+H]^+$.

1-(2-(6-Chloro-1H-benzo[d]imidazol-2-yl)phenoxy)-4-methoxy-4-oxobutane-2-sulfonic acid (5b). Off white amorphous solid (144 mg, 68% yield); ^{1}H NMR (500 MHz, CD_3OD) δ 8.13 (d, *J* = 7.8 Hz, 1H), 7.76 (d, *J* = 1.7 Hz, 1H), 7.72 – 7.67 (m, 1H), 7.60 (t, *J* = 7.9 Hz, 1H), 7.37 (d, *J* = 8.7 Hz, 1H), 7.26 – 7.19 (m, 2H), 4.76 – 4.71 (m, 1H), 4.58 (dd, *J* = 9.7, 5.8 Hz, 1H), 3.85 – 3.77 (m, 1H), 3.69 (s, 3H), 3.24 (dd, *J* = 17.1, 4.2 Hz, 1H), 2.86 (dd, *J* = 17.1, 9.6 Hz, 1H); ^{13}C{^{1}H} NMR (125 MHz, CD_3OD+$CDCl_3$) δ 171.9, 156.6, 147.9, 134.3, 132.2, 130.65, 130.61, 129.2, 125.4, 121.8, 115.1, 114.0, 112.8, 112.4, 67.6, 55.3, 51.6, 31.8; HRMS (ESI-TOF): m/z calcd for $C_{18}H_{18}ClN_2O_6S$, 425.0574 found 425.0570 $[M+H]^+$.

1-(2-(1H-Benzo[d]imidazol-2-yl)phenoxy)-4-methoxy-4-oxobutane-2-sulfonic acid (5c). Off white amorphous solid (126 mg, 65% yield); ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.22 (dd, *J* = 7.8, 1.2 Hz, 1H), 7.78 (dd, *J* = 6.1, 3.1 Hz, 2H), 7.75 – 7.67 (m, 1H), 7.54 (dd, *J* = 6.1, 3.1 Hz, 2H), 7.42 (d, *J* = 8.5 Hz, 1H), 7.35 – 7.26 (m, 1H), 4.64 (dd, *J* = 9.7, 2.5 Hz, 1H), 4.45 (dd, *J* = 9.7, 6.0 Hz, 1H), 3.60 (s, 3H), 3.48 – 3.42 (m, 1H), 2.97 (dd, *J* = 16.7, 4.8 Hz, 1H), 2.70 (dd, *J* = 16.7, 8.8 Hz, 1H); ^{13}C{^{1}H} NMR (125 MHz, DMSO-d_6) δ 172.0, 156.9, 146.5, 135.2, 132.8, 130.1, 125.8, 122.0, 114.5, 113.5, 112.3, 68.8, 55.0, 52.1, 32.6. HRMS (ESI-TOF): m/z calcd for $C_{18}H_{19}N_2O_6S$, 391.0963 found 391.0963 $[M+H]^+$.

General reaction procedure for the preparation of compounds 5d-e. Sodium bisulfite (0.5 mmol) in H_2O (0.5 mL) was added to a solution of aldehyde (**1a**, 0.5 mmol) in DMF (2 mL) at rt. After 30 min, 2-aminothiophenol (**3**, 0.5 mmol) was added and stirring was continued at rt for 2 h. The reaction mixture was heated at 70 ºC for 8 h. After completion of step-1, another one equivalent of sodium bisulfite (0.5 mmol) in H_2O (0.5 mL) was added and the reaction was heated to 70 °C for 8-12 h. After completion, the reaction mixture was diluted with EtOAc (20 mL) and treated with water (10 mL). The aqueous layer was concentrated to minimum volume. Crystallization of the crude mixture from water produced pure product.

1-(2-(Benzo[d]thiazol-2-yl)phenoxy)-4-methoxy-4-oxobutane-2-sulfonic acid (5d). White amorphous solid (134 mg, 66% yield); ^{1}H NMR (500 MHz, CD_3OD) δ 8.40 (d, *J* = 7.8 Hz, 1H), 8.03 (d, *J* = 8.2 Hz, 1H), 7.98 (d, *J* = 7.8 Hz, 1H), 7.56 – 7.48 (m, 2H), 7.42 (t, *J* = 7.5 Hz, 1H), 7.28 (d, *J* = 8.3 Hz, 1H), 7.17 (t, *J* = 7.5 Hz, 1H), 4.87 – 4.83 (m, 1H), 4.43 (t, *J* = 9.9 Hz, 1H), 4.09 – 4.02 (m, 1H), 3.58 (s, 3H), 3.07 (d, *J* = 6.4 Hz, 2H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 173.4, 164.0, 156.3, 151.7, 135.7, 132.5, 129.8, 126.5, 125.2, 122.6, 122.0, 121.8, 121.5, 112.9, 68.3, 56.2, 52.1, 34.2; HRMS (ESI-TOF): m/z calcd for $C_{18}H_{18}NO_6S_2$, 408.0575 found 408.0571 $[M+H]^+$.

1-(2-(6-Chlorobenzo[d]thiazol-2-yl)phenoxy)-4-methoxy-4-oxobutane-2-sulfonic acid (5e). White amorphous solid (136 mg, 62% yield); ^{1}H NMR (500 MHz, CD_3OD) δ 8.45 (dd, *J* = 7.9, 1.7 Hz, 1H), 8.01 (dd, *J* = 10.8, 5.2 Hz, 2H), 7.59 – 7.55 (m, 1H), 7.43 (dd, *J* = 8.0, 2.0 Hz, 1H), 7.32 (d, *J* = 8.0 Hz, 1H), 7.23 – 7.16 (m, 1H), 4.85 – 4.80 (m, 1H), 4.49 – 4.41 (m, 1H), 4.07 – 3.99 (m, 1H), 3.58 (s, 3H), 3.12 – 3.00 (m, 2H); ^{13}C{^{1}H} NMR (125 MHz, CD_3OD) δ 172.2, 165.5, 156.3, 152.7, 134.3, 132.4, 131.8, 129.0, 124.9, 122.3, 121.5 (2C), 121.2, 112.7, 68.4, 55.9, 50.9, 33.7; HRMS (ESI-TOF): m/z calcd for $C_{18}H_{17}ClNO_6S_2$, 442.0185 found 442.0184 $[M+H]^+$.

General reaction procedure for the preparation of compounds 6a-c. To a stirred solution of amine (**2**, 0.25 mmol) and molecular sieves in ACN (1 mL), a solution of aldehyde (**1a**, 0.25 mmol) in ACN (1 mL) was added over a period of 1h at rt. After 2h, $Sc(OTf)_3$ (10 mol%) was added and stirring was continued at rt for another 10h. Next, the reaction mixture was stirred under MW at 70-100 °C for 1h. TLC showed the complete absence of starting materials and formation of new spots. Next, $Sc(OTf)_3$ (10 mol%) was added and the reaction mixture was stirred under MW conditions at 100-130°C for 1.5h. After completion, ACN was removed, and the crude was purified by flash chromatography, using EtOAc in hexane as an eluent.

Methyl 2-(6,7-dihydrobenzo[f]benzo[4,5]imidazo[1,2-*d*][1,4]oxazepin-7-yl)acetate (6a). Off white solid (50 mg, 65% yield, eluent: 19% EtOAc in hexane); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.86 (dd, *J* = 8.1, 1.6 Hz, 1H), 7.87 – 7.82 (m, 1H), 7.47 – 7.43 (m, 1H), 7.42 – 7.37 (m, 1H), 7.37 – 7.30 (m, 2H), 7.24 – 7.18 (m, 1H), 7.14 (dd, *J* = 8.2, 0.9 Hz, 1H), 5.26 – 5.20 (m, 1H), 4.94 (dd, *J* = 13.1, 3.5 Hz, 1H), 4.35 (d, *J* = 13.1 Hz, 1H), 3.75 (s, 3H), 3.19 (dd, *J* = 16.8, 9.3 Hz, 1H), 2.89 (dd, *J* = 16.8, 4.0 Hz, 1H); ^{13}C{^{1}H}

NMR (125 MHz, $CDCl_3$) δ 171.1, 156.6, 149.8, 142.9, 135.6, 132.1, 131.6, 123.2, 123.1, 123.0, 120.8, 120.0, 117.7, 109.4, 70.2, 53.5, 52.3, 35.4; HRMS (ESI-TOF): m/z calcd for $C_{18}H_{17}N_2O_3$, 309.1239 found 309.1221 $[M+H]^+$.

Methyl 2-(10,11-dimethyl-6,7-dihydrobenzo[f]benzo[4,5]imidazo[1,2-*d*][1,4]oxazepin-7-yl) acetate (6b). Off white solid (60 mg, 72% yield, eluent: 21% EtOAc in hexane); ^1H NMR (500 MHz, $CDCl_3$) δ 8.82 (dd, *J* = 8.2, 1.7 Hz, 1H), 7.60 (s, 1H), 7.39 – 7.34 (m, 1H), 7.23 – 7.15 (m, 2H), 7.12 (dd, *J* = 8.2, 1.1 Hz, 1H), 5.18 – 5.12 (m, 1H), 4.92 (dd, *J* = 13.1, 3.4 Hz, 1H), 4.32 (d, *J* = 13.1 Hz, 1H), 3.77 (s, 3H), 3.17 (dd, *J* = 16.8, 9.7 Hz, 1H), 2.91 – 2.85 (m, 1H), 2.44 (s, 3H), 2.42 (s, 3H); ^{13}C NMR{^1H} (125 MHz, $CDCl_3$) δ 171.0, 156.3, 148.8, 141.4, 134.0, 132.4, 132.0, 131.7, 131.0, 122.8, 120.6, 119.9, 117.9, 109.4, 70.0, 53.3, 52.2, 35.2, 20.7, 20.3; HRMS (ESI-TOF): m/z calcd for $C_{20}H_{21}N_2O_3$, 337.1552 found 337.1525 $[M+H]^+$.

Methyl 2-(10,11-dichloro-6,7-dihydrobenzo[f]benzo[4,5]imidazo[1,2-*d*][1,4]oxazepin-7-yl) acetate (6c). White solid (45 mg, 48% yield, eluent: 23% EtOAc in hexane); ^1H NMR (500 MHz, $CDCl_3$) δ 8.77 (dd, *J* = 8.2, 1.7 Hz, 1H), 7.90 (s, 1H), 7.55 (s, 1H), 7.47 – 7.38 (m, 1H), 7.24 – 7.19 (m, 1H), 7.14 (dd, *J* = 8.2, 1.1 Hz, 1H), 5.16 – 5.11 (m, 1H), 4.93 (dd, *J* = 13.1, 3.5 Hz, 1H), 4.32 (d, *J* = 13.1 Hz, 1H), 3.77 (s, 3H), 3.17 (dd, *J* = 16.9, 8.8 Hz, 1H), 2.84 (ddd, *J* = 16.9, 5.1, 0.8 Hz, 1H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 170.7, 156.7, 151.8, 142.3, 134.8, 132.3, 132.2, 127.3, 127.0, 123.2, 121.1, 120.9, 116.9, 110.9, 70.1, 53.8, 52.5, 35.3; HRMS (ESI-TOF): m/z calcd for $C_{18}H_{15}Cl_2N_2O_3$, 377.04597 found 377.0441 $[M+H]^+$.

Methyl (*E*)-4-((1-formylnaphthalen-2-yl)oxy)but-2-enoate (1b).[16c] NaH (6 mmol) at 0 °C was added to a solution of 2-hydroxy-1-naphthaldehyde (5 mmol) in DMF (10 mL). After 30 min, a solution of methyl *trans*-4-bromo-2-butenoate (7.0 mmol) in DMF (5 mL) was added dropwise and stirring was continued at rt for 3h. After completion, reaction mixture was quenched with saturated NH_4Cl solution, diluted with ethylacetate (100 mL) and washed with cold water (2 x 50 mL). The organic layer was separated, dried over Na_2SO_4 and concentrated under vacuum. The crude was purified on flash chromatography, using 28% EtOAc in hexane as an eluent to produce the title compound **1b**. Off White solid (1.21g, 90% yield); ^1H NMR (500 MHz, $CDCl_3$) δ 10.99 (s, 1H), 9.29 (d, *J* = 8.7 Hz, 1H), 8.07 (d, *J* = 9.1 Hz, 1H), 7.80 (d, *J* = 8.0 Hz, 1H), 7.69 – 7.63 (m, 1H), 7.47 (t, *J* = 7.5 Hz, 1H), 7.26 – 7.08 (m, 2H), 6.27 (dd, *J* = 15.8, 1.7 Hz, 1H), 4.98 (s, 2H), 3.80 (s, 3H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 191.6, 166.3, 162.3, 141.5, 137.7, 131.6, 130.2, 129.0, 128.4, 125.3, 125.2, 122.4, 117.4, 113.3, 67.9, 52.0; LCMS (ESI): m/z 271 $[M+H]^+$.

General reaction procedure for the preparation of compounds 6d-f. To a stirred solution of amine (**2**, 0.25 mmol) and molecular sieves in ACN (1 mL), a solution of aldehyde (**1b**, 0.25 mmol) in ACN (1 mL) was added over a period of 1h at rt. After 2h, $Sc(OTf)_3$ (10 mol%) was added and stirring was continued at rt for another 10h. Next, the reaction mixture is stirred under MW conditions at 70-100 °C for 1h. TLC showed the complete absence of starting materials and formation of new spots. Next, $Sc(OTf)_3$ (10 mol%) was added and the reaction mixture was continued at 130-150°C for 1.5h. After completion, ACN was removed, and the crude was purified by flash chromatography, using EtOAc in hexane as an eluent.

Methyl 2-(8,9-dihydrobenzo[4,5]imidazo[1,2-*d*]naphtho[1,2-*f*][1,4]oxazepin-9-yl) acetate (6d). Yellowish solid (47 mg, 53% yield, eluent: 24% EtOAc in hexane); ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.14 (d, *J* = 8.7 Hz, 1H), 7.95 (dd, *J* = 6.8, 1.7 Hz, 1H), 7.90 (d, *J* = 8.7 Hz, 1H), 7.85 (d, *J* = 8.0 Hz, 1H), 7.63 – 7.56 (m, 2H), 7.52 – 7.46 (m, 1H), 7.42 – 7.35 (m, 2H), 7.28 (d, *J* = 8.8 Hz, 1H), 5.41 – 5.31 (m, 1H), 4.72 – 4.60 (m, 2H), 3.59 (s, 3H), 2.82 (d, *J* = 7.1 Hz, 2H). ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 170.8, 155.1, 149.0, 143.2, 134.9, 132.7 (2C), 131.1, 128.1, 128.0, 127.2, 125.4, 123.4, 122.9, 120.8, 120.3, 114.9, 109.7, 75.1, 52.3, 51.7, 37.0; HRMS (ESI-TOF): m/z calcd for $C_{22}H_{19}N_2O_3$, 359.1395 found 359.1367 $[M+H]^+$.

Methyl 2-(12,13-dimethyl-8,9-dihydrobenzo[4,5]imidazo[1,2-*d*]naphtho[1,2-*f*][1,4] oxazepin-9-yl)acetate (6e). Off white solid (54 mg, 56% yield, eluent: 26% EtOAc in hexane); ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.16 (d, *J* = 8.6 Hz, 1H), 7.91 – 7.84 (m, 2H), 7.71 (s, 1H), 7.63 – 7.59 (m, 1H), 7.53 – 7.47 (m, 1H), 7.34 (s, 1H), 7.29 (t, *J* = 4.4 Hz, 1H), 5.34 – 5.26 (m, 1H), 4.65 (dd, *J* = 3.8, 1.7 Hz, 2H), 3.63 (s, 3H), 2.83 (d, *J* = 7.1 Hz, 2H), 2.49 (s, 3H), 2.46 (s, 3H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 171.0, 154.9, 148.2, 142.1, 133.5, 132.8, 132.6, 132.3, 131.7, 131.1, 128.1, 127.8, 127.4, 125.3, 120.8, 120.3, 115.3, 109.8, 74.9, 52.3, 51.7, 36.9, 20.9, 20.4; HRMS (ESI-TOF): m/z calcd for $C_{24}H_{23}N_2O_3$, 387.1708 found 387.1681 $[M+H]^+$.

Methyl 2-(12,13-dichloro-8,9-dihydrobenzo[4,5]imidazo[1,2-*d*]naphtho[1,2-*f*][1,4] oxazepin-9-yl)acetate (6f). Brownish solid (43 mg, 41% yield, eluent: 27% EtOAc in hexane); ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.07 (d, *J* = 8.7 Hz, 1H), 8.02 (s, 1H), 7.95 (d, *J* = 8.8 Hz, 1H), 7.88 (d, *J* = 8.0 Hz, 1H), 7.71 (s, 1H), 7.66 – 7.61 (m, 1H), 7.55 – 7.51 (m, 1H), 7.30 (d, *J* = 8.9 Hz, 1H), 5.30 – 5.22 (m, 1H), 4.67 (dd, *J* = 5.5, 3.9 Hz, 2H), 3.63 (s, 3H), 2.82 (dd, *J* = 7.1, 3.0 Hz, 2H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 170.5, 155.2, 151.1, 142.6, 134.3, 133.3, 132.5, 131.1, 128.3, 128.2, 127.4, 127.0, 126.9, 125.6, 121.3, 120.8, 114.3, 111.3, 74.9, 52.4, 52.2, 36.8; HRMS (ESI-TOF): m/z calcd for $C_{22}H_{17}Cl_2N_2O_3$, 427.0616 found 427.0589 $[M+H]^+$.

Methyl (*E*)-4-((9-formyl-2,3,6,7-tetrahydro-1H,5H-pyrido[3,2,1-ij]quinolin-8-yl)oxy)but-2-enoate (1c). NaH (6 mmol) at 0 °C was added to a solution of 8-hydroxy-2,3,6,7-tetrahydro-1H,5H-pyrido[3,2,1-

ij]quinoline-9-carbaldehyde (5 mmol) in DMF (10 mL). After 30 min, a solution of methyl *trans*-4-bromo-2-butenoate (7.0 mmol) in DMF (5 mL) was added dropwise and stirring was continued at rt for 3h. After completion, reaction mixture was quenched saturated NH_4Cl solution, diluted with ethylacetate (100 mL) and washed with cold water (2 x 50 mL). The organic layer was separated, dried over Na_2SO_4 and concentrated under vacuum. The crude was purified on flash chromatography, using 35% EtOAc in hexane as an eluent to produce the title compound **1c**. Yellowish solid (1.57g, 74% yield); ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.94 (s, 1H), 7.33 (s, 1H), 7.13 – 7.07 (m, 1H), 6.35 – 6.29 (m, 1H), 4.58 (dd, *J* = 4.2, 2.1 Hz, 2H), 3.79 (s, 3H), 3.39 – 3.24 (m, 4H), 2.76 – 2.70 (m, 4H), 2.10 – 1.87 (m, 4H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 187.3, 166.7, 158.7, 149.1, 142.9, 127.8, 121.4, 117.6, 116.9, 112.5, 73.4, 51.8, 50.2, 49.8, 27.4, 21.4, 21.1, 20.8; LCMS (ESI): m/z 316 $[M+H]^+$.

General reaction procedure for the preparation of compounds 6g-i. To a stirred solution of amine (**2**, 0.25 mmol) and molecular sieves in ACN (1 mL), a solution of aldehyde (**1c**, 0.25 mmol) in ACN (1 mL) was added over a period of 1h at rt. After 2h, $Sc(OTf)_3$ (10 mol%) was added and stirring was continued at rt for another 10h. TLC showed the complete absence of starting materials and formation of new spots. Next, $Sc(OTf)_3$ (10 mol%) was added and the stirring was continued at rt for another 12h. After completion, ACN was removed, and the crude was purified by flash chromatography, using EtOAc in hexane as an eluent.

Methyl 2-(2,3,6,7,9,10-hexahydro-1H,5H-benzo[4',5']imidazo[1',2':4,5][1,4] oxazepino[7,6-*f*]pyrido[3,2,1-*ij*]quinolin-10-yl)acetate (6g). Brownish solid (68 mg, 68% yield, eluent: 34% EtOAc in hexane); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.26 (s, 1H), 7.80 – 7.74 (m, 1H), 7.35 (d, *J* = 7.4 Hz, 1H), 7.30 – 7.19 (m, 2H), 5.16 – 5.09 (m, 1H), 4.88 (dd, *J* = 12.9, 3.3 Hz, 1H), 4.29 (d, *J* = 12.9 Hz, 1H), 3.75 (s, 3H), 3.26 – 3.14 (m, 5H), 2.92 – 2.76 (m, 5H), 2.05 – 1.94 (m, 4H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 171.4, 153.7, 151.5, 145.5, 143.2, 135.4, 129.0, 122.6, 121.7, 118.9, 117.0, 110.0, 108.8, 104.9, 69.8, 53.4, 52.2, 50.1, 49.4, 35.2, 27.4, 22.1, 21.8, 21.5; HRMS (ESI-TOF): m/z calcd for $C_{24}H_{26}N_3O_3$, 404.1974 found 404.1943 $[M+H]^+$.

Methyl 2-(13,14-dimethyl-2,3,6,7,9,10-hexahydro-1H,5H-benzo[4',5']imidazo[1',2':4,5] [1,4] oxazepino[7,6-*f*]pyrido[3,2,1-*ij*]quinolin-10-yl)acetate (6h). Brownish solid (77 mg, 72% yield, eluent: 34% EtOAc in hexane); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.14 (s, 1H), 7.43 (s, 1H), 6.99 (s, 1H), 4.98 – 4.91 (m, 1H), 4.76 (dd, *J* = 12.9, 3.2 Hz, 1H), 4.17 (d, *J* = 12.9 Hz, 1H), 3.67 (s, 3H), 3.16 – 3.03 (m, 5H), 2.81 – 2.65 (m, 5H), 2.32 (s, 3H), 2.29 (s, 3H), 1.95 – 1.85 (m, 4H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 171.5, 153.5, 150.7, 145.2, 141.8, 133.9, 131.2, 130.8, 128.8, 119.2, 117.0, 110.1, 109.1, 105.4, 69.8, 53.4, 52.2, 50.1, 49.4, 35.1, 27.3, 22.2, 21.8, 21.6, 20.7, 20.4; HRMS (ESI-TOF): m/z calcd for $C_{26}H_{30}N_3O_3$, 432.2287 found 432.2262 $[M+H]^+$.

Methyl 2-(13,14-dichloro-2,3,6,7,9,10-hexahydro-1H,5H-benzo[4',5']imidazo [1',2':4,5][1,4] oxazepino[7,6-*f*]pyrido[3,2,1-*ij*]quinolin-10-yl)acetate (6i). Brownish solid (73 mg, 62% yield, eluent: 36% EtOAc in hexane); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.12 (s, 1H), 7.75 (s, 1H), 7.39 (s, 1H), 5.01 – 4.96 (m, 1H), 4.83 (dd, *J* = 13.0, 3.3 Hz, 1H), 4.24 (d, *J* = 13.0 Hz, 1H), 3.74 (s, 3H), 3.26 – 3.09 (m, 5H), 2.82 – 2.71 (m, 5H), 2.01 – 1.91 (m, 4H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 171.0, 153.8, 153.6, 146.0, 142.8, 134.8, 129.0, 126.5, 125.2, 119.8, 117.1, 110.1, 109.9, 103.9, 69.7, 53.7, 52.4, 50.1, 49.4, 35.1, 27.4, 22.0, 21.7, 21.4; HRMS (ESI-TOF): m/z calcd for $C_{24}H_{24}Cl_2N_3O_3$, 472.1194 found 472.1171 $[M+H]^+$.

Methyl (*E*)-4-((N-(2-formylphenyl)-4-methylphenyl)sulfonamido)but-2-enoate (1d).[16c] K_2CO_3 (4 mmol) at rt was added to a solution of *N*-(2-formylphenyl)-4-methylbenzenesulfonamide (2 mmol) in ACN (8 mL). After 30 min, methyl *trans*-4-bromo-2-butenoate (2.2 mmol) was added dropwise and stirring was continued at rt for 12h. After completion, reaction mixture was filtered and ACN was removed. The crude was dissolved in ethylacetate (100 mL) and washed with water (2 x 50 mL). The organic layer was separated, dried over Na_2SO_4 and concentrated under vacuum. The crude was purified on flash chromatography, using 33% EtOAc in hexane as an eluent to produce the title compound **1d**. Yellowish solid (611 mg, 82% yield); ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.38 (s, 1H), 8.07 – 7.97 (m, 1H), 7.54 – 7.45 (m, 4H), 7.35 – 7.24 (m, 3H), 6.87 – 6.73 (m, 2H), 5.85 (td, *J* = 15.6, 1.4 Hz, 1H), 3.70 (s, 3H), 2.47 (s, 3H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 189.6, 165.7, 144.7, 141.1, 140.9, 135.8, 134.4, 134.1, 129.9, 129.2, 129.1, 128.1, 128.0, 125.0, 52.5, 51.9, 21.7; LCMS (ESI): m/z 374 $[M+H]^+$.

General reaction procedure for the preparation of compounds 6j-l. To a stirred solution of amine (**2**, 0.25 mmol) and molecular sieves in ACN (1 mL), a solution of aldehyde (**1d**, 0.25 mmol) in ACN (1 mL) was added over a period of 1h at rt. After 2h, $Sc(OTf)_3$ (10 mol%) was added and stirring was continued at rt for another 10h. Next, the reaction mixture is stirred under MW conditions at 70-100 °C for 1h. TLC showed the complete absence of starting materials and formation of new spots. Next, $Sc(OTf)_3$ (10 mol%) was added and the reaction mixture was continued at 100-130°C for 1.5h. After completion, ACN was removed, and the crude was purified by flash chromatography, using EtOAc in hexane as an eluent.

Methyl 2-(5-tosyl-6,7-dihydro-5H-benzo[f]benzo[4,5]imidazo[1,2-*d*][1,4]diazepin-7-yl)acetate (6j). Off white solid (66 mg, 58% yield, eluent: 27% EtOAc in hexane); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.16 (dd, *J* = 7.3, 1.7 Hz, 1H), 7.74 – 7.69 (m, 1H), 7.65 (d, *J* = 7.6 Hz, 1H), 7.61 – 7.51 (m, 2H), 7.30 – 7.21 (m, 2H), 7.17 – 7.12 (m, 1H), 7.11 – 7.04 (m, 2H), 6.55 (d, *J* = 8.0 Hz, 2H), 5.14 (dd, *J* = 7.9, 4.6 Hz, 1H), 5.03 (dd, *J* = 15.3, 7.9 Hz, 1H), 3.88 (dd, *J* = 15.3, 7.4 Hz, 1H), 3.52 (s, 3H), 2.63 (dd, *J* = 16.4, 4.6 Hz, 1H), 2.52 (dd, *J* = 16.4, 8.3 Hz, 1H), 1.90 (s, 3H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 169.8, 149.6, 143.4, 138.3, 136.2, 134.7, 131.4, 131.2, 130.7, 129.6, 129.2, 125.7, 123.4, 123.1, 119.9, 114.2, 109.9, 54.9, 52.3, 50.5, 38.7, 21.4; HRMS (ESI-TOF): m/z calcd for $C_{25}H_{24}N_3O_4S$, 462.1487 found 462.1472 $[M+H]^+$.

Methyl 2-(10,11-dimethyl-5-tosyl-6,7-dihydro-5H-benzo[f]benzo[4,5]imidazo[1,2-*d*][1,4]diazepin-7-yl)acetate (6k). Yellowish solid (78 mg, 64% yield, eluent: 28% EtOAc in hexane); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.17 (s, 1H), 7.70 (d, *J* = 4.9 Hz, 1H), 7.56 (d, *J* = 2.7 Hz, 2H), 7.43 (s, 1H), 7.11 (d, *J* = 7.5 Hz, 2H), 6.87 (s, 1H), 6.57 (d, *J* = 7.3 Hz, 2H), 5.13 – 4.92 (m, 2H), 3.87 (dd, *J* = 14.6, 6.9 Hz, 1H), 3.57 (s, 3H), 2.65 (d, *J* = 13.4 Hz, 1H), 2.52 (dd, *J* = 16.3, 8.1 Hz, 1H), 2.43 (s, 3H), 2.39 (s, 3H), 1.90 (s, 3H). ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 169.9, 148.6, 143.1, 138.3 (2C), 136.4 (2C), 133.1, 132.7, 132.1, 131.1, 131.0, 130.5, 129.5, 129.2, 125.7, 119.8, 110.1, 54.8, 52.3, 50.4, 38.6, 21.1, 20.8, 20.3. LCMS (ESI): m/z 490 $[M+H]^+$.

Methyl 2-(10,11-dichloro-5-tosyl-6,7-dihydro-5H-benzo[f]benzo[4,5]imidazo[1,2-*d*][1,4]diazepin-7-yl)acetate (6l). Off white solid (53 mg, 40% yield, eluent: 30% EtOAc in hexane); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.13 (dd, *J* = 7.6, 1.6 Hz, 1H), 7.77 – 7.70 (m, 2H), 7.66 – 7.57 (m, 2H), 7.24 (s, 1H), 7.14 (d, *J* = 8.0 Hz, 2H), 6.68 (d, *J* = 8.0 Hz, 2H), 5.06 – 4.96 (m, 2H), 3.94 – 3.85 (m, 1H), 3.56 (s, 3H), 2.61 – 2.54 (m, 2H), 2.02 (s, 3H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 169.4, 151.8, 143.5, 136.5 (2C), 133.9, 132.1, 131.4, 130.6, 129.8, 129.4, 128.9, 127.4, 127.3, 125.8, 120.9, 111.4, 54.7, 52.4, 50.8, 38.5, 21.2; HRMS (ESI-TOF): m/z calcd for $C_{25}H_{22}Cl_2N_3O_4S$, 530.0708 found 530.0687 $[M+H]^+$.

Regioisomers 6m and 6n. To a stirred solution of amine (**2i**, 0.25 mmol) and molecular sieves in ACN (1 mL), a solution of aldehyde (**1a**, 0.25 mmol) in ACN (1 mL) was added over a period of 1h at rt. After 2h, $Sc(OTf)_3$ (10 mol%) was added and stirring was continued at rt for another 10h. Next, the reaction mixture is stirred under MW conditions at 70-100 °C for 1h. TLC showed the complete absence of starting materials and formation of new spots. Next, $Sc(OTf)_3$ (10 mol%) was added and the reaction mixture was continued at 100-130°C for 1.5h. After completion, ACN was removed, and the crude was purified by flash chromatography, using 20% EtOAc in hexane as an eluent. Off white amorphous solid (mixture of two regioisomers, 43 mg, 51% yield); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.77 (two s, 2H), 7.77 (d, *J* = 1.8 Hz, 1H), 7.71 (d, *J* = 8.6 Hz, 1H), 7.43 – 7.31 (m, 4H), 7.29 – 7.23 (m, 2H), 7.21 – 7.14 (m, 2H), 7.11 (d, *J* = 8.2 Hz, 2H), 5.20 – 5.09 (m, 2H), 4.93 – 4.87 (m, 2H), 4.30 (dd, *J* = 13.1, 1.1 Hz, 2H), 3.73 (two s, 6H), 3.18 – 3.10 (m, 2H), 2.87 – 2.79 (m, 2H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ (170.9, 170.8) 1C, (156.6, 156.6) 1C, (151.0, 150.7) 1C, (143.6, 141.4) 1C, (136.1, 134.2) 1C, (132.1, 132.0) 1C, (132.0, 131.9) 1C, (128.9, 128.8) 1C, (123.9, 123.5) 1C, (123.1, 123.1) 1C, (120.8, 120.8) 1C, (120.8,119.6) 1C, (117.2, 117.1) 1C, (110.3, 109.6) 1C, (70.1, 70.1) 1C, (53.7, 53.7) 1C, (52.4, 52.4) 1C, (35.4, 35.3) 1C; LCMS (ESI): m/z 343 $[M+H]^+$.

General reaction procedure for the preparation of compounds 8a-c. Aldehyde (**1a**, 0.25 mmol) and benzamide (**7a-c**, 0.25 mmol) were mixed in the presence of molecular sieves in ACN (1 mL) at rt. After 2h, a 10 mol% $Sc(OTf)_3$ was added, and stirring was continued at rt for another 10h. Next, the reaction

mixture is stirred in a MW reactor at 70-100 °C for 1h. TLC showed the complete absence of starting materials and formation of new spots. Next, $Sc(OTf)_3$ (10 mol%) was added and the stirring was continued under MW at 100-150°C for 1.5h. After completion, ACN was removed, and the crude was purified by flash chromatography, using EtOAc in hexane as an eluent.

Methyl 2-(9-oxo-6,7-dihydro-9H-benzo[6,7][1,4]oxazepino[5,4-*b*]quinazolin-7-yl)acetate (8a). White solid (48 mg, 58% yield, eluent: 26% EtOAc in hexane); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.32 (d, *J* = 7.7 Hz, 2H), 7.83 – 7.77 (m, 2H), 7.56 – 7.45 (m, 1H), 7.21 (t, *J* = 7.5 Hz, 1H), 7.10 (d, *J* = 8.2 Hz, 1H), 6.15 – 6.08 (m, 1H), 4.80 (dd, *J* = 12.7, 4.5 Hz, 1H), 4.49 (dd, *J* = 12.7, 1.6 Hz, 1H), 3.69 (s, 3H), 2.77 – 2.58 (m, 2H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 170.5, 161.7, 155.8, 152.6, 147.8, 134.8, 133.9, 133.4, 127.8, 127.3, 127.2, 123.0, 122.5, 120.4, 119.4, 72.4, 52.2, 49.4, 34.2; HRMS (ESI-TOF): m/z calcd for $C_{19}H_{17}N_2O_4$, 337.1188 found 337.1179 $[M+H]^+$.

Methyl 2-(11-methoxy-9-oxo-6,7-dihydro-9H-benzo[6,7][1,4]oxazepino[5,4-*b*]quinazolin-7-yl)acetate (8b). White solid (57 mg, 63% yield, eluent: 29% EtOAc in hexane); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.28 (d, *J* = 7.7 Hz, 1H), 7.73 (d, *J* = 8.9 Hz, 1H), 7.67 (d, *J* = 2.4 Hz, 1H), 7.47 (t, *J* = 7.2 Hz, 1H), 7.40 (dd, *J* = 8.8, 2.6 Hz, 1H), 7.20 (t, *J* = 7.4 Hz, 1H), 7.09 (d, *J* = 8.1 Hz, 1H), 6.13 (d, *J* = 2.0 Hz, 1H), 4.79 (dd, *J* = 12.6, 4.4 Hz, 1H), 4.49 (d, *J* = 12.6 Hz, 1H), 3.96 (s, 3H), 3.69 (s, 3H), 2.72 (dd, *J* = 16.6, 8.9 Hz, 1H), 2.62 (dd, *J* = 16.6, 6.1 Hz, 1H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 170.5, 161.6, 158.8, 155.6, 150.4, 142.5, 133.7, 133.1, 129.4, 125.2, 123.0, 122.5, 120.4, 120.2, 106.4, 72.4, 56.0, 52.2, 49.4, 34.3; HRMS (ESI-TOF): m/z calcd for $C_{20}H_{19}N_2O_5$, 367.1293 found 367.1279 $[M+H]^+$.

Methyl 2-(11-chloro-9-oxo-6,7-dihydro-9H-benzo[6,7][1,4]oxazepino[5,4-*b*]quinazolin-7-yl)acetate (8c). White solid (38 mg, 41% yield, eluent: 27% EtOAc in hexane); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.34 – 8.25 (m, 2H), 7.74 (s, 2H), 7.51 (dd, *J* = 11.1, 4.1 Hz, 1H), 7.21 (t, *J* = 7.4 Hz, 1H), 7.11 (d, *J* = 8.1 Hz, 1H), 6.13 – 6.03 (m, 1H), 4.80 (dd, *J* = 12.8, 4.6 Hz, 1H), 4.47 (dd, *J* = 12.8, 1.9 Hz, 1H), 3.69 (s, 3H), 2.72 (dd, *J* = 16.6, 8.9 Hz, 1H), 2.62 (dd, *J* = 16.6, 6.3 Hz, 1H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 170.2, 160.7, 155.7, 152.7, 146.2, 135.1, 133.7, 133.4, 132.8, 129.4, 126.4, 123.0, 122.1, 120.4, 120.3, 72.3, 52.2, 49.5, 33.9. HRMS (ESI-TOF): m/z calcd for $C_{19}H_{16}ClN_2O_4$, 371.0798 found 371.0783 $[M+H]^+$.

Methyl 2-(11-oxo-8,9-dihydro-11H-naphtho[1',2':6,7][1,4]oxazepino[5,4-*b*]quinazolin-9-yl)acetate (8d). Aldehyde (**1b**, 0.25 mmol) and benzamide (**7a**, 0.25 mmol) were mixed in the presence of molecular sieves in ACN (1 mL) at rt. After 2h, a 10 mol% of $Sc(OTf)_3$ was added, and stirring was continued at rt for another 10h. Next, the reaction mixture is stirred in a MW reactor at 70-100 °C for 1h. TLC showed the complete absence of starting materials and formation of new spots. Next, $Sc(OTf)_3$ (10 mol%) was added and the stirring was continued under MW at 100-150°C for 1.5h. After completion, ACN was removed,

and the crude was purified by flash chromatography, using 27% of EtOAc in hexane as an eluent. White solid (23 mg, 24% yield); ^{1}H NMR (500 MHz, CDCl3) δ 8.44 (d, *J* = 7.1 Hz, 2H), 8.05 (d, *J* = 8.7 Hz, 1H), 7.93 (d, *J* = 8.0 Hz, 1H), 7.83 (s, 2H), 7.66 – 7.53 (m, 3H), 7.34 (d, *J* = 8.7 Hz, 1H), 6.42 – 6.33 (m, 1H), 4.91 – 4.82 (m, 1H), 4.40 (d, *J* = 11.7 Hz, 1H), 3.53 (s, 3H), 2.29 – 2.12 (m, 2H). ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 170.4, 161.6, 153.8, 151.3, 147.3, 134.9, 134.0, 132.1, 131.8, 128.6, 128.3, 127.8, 127.6 (2C), 126.1, 125.6, 123.5, 120.8, 120.2, 76.8, 52.1, 46.1, 38.5. LCMS (ESI): m/z 387 $[M+H]^+$.

Methyl 2-(8-oxo-2,3,5,6,16,17-hexahydro-1H,8H,15H-pyrido[3'',2'',1'':8',1']quinolino[6',5':6,7][1,4]oxazepino[5,4-*b*]quinazolin-6-yl)acetate (8e). Aldehyde (**1c**, 0.25 mmol) and benzamide (**7a**, 0.25 mmol) were mixed in the presence of molecular sieves in ACN (1 mL) at rt. After 2h, a 10 mol% $Sc(OTf)_3$ was added, and stirring was continued at rt for another 10h. Next, the reaction mixture is stirred in a MW reactor at 70-100 °C for 1h. TLC showed the complete absence of starting materials and formation of new spots. Next, $Sc(OTf)_3$ (10 mol%) was added and the stirring was continued under MW at 100-130°C for 1.5h. After completion, ACN was removed, and the crude was purified by flash chromatography, using 31% of EtOAc in hexane as an eluent. Brownish solid (56 mg, 52% yield); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.17 (d, *J* = 7.5 Hz, 1H), 7.84 – 7.56 (m, 3H), 7.32 (s, 1H), 6.03 – 5.88 (s, 1H), 4.57 (d, *J* = 9.6 Hz, 1H), 4.35 (d, *J* = 11.8 Hz, 1H), 3.58 (s, 3H), 3.27 – 3.05 (m, 4H), 2.84 – 2.50 (m, 6H), 1.99 – 1.75 (m, 4H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 170.9, 158.6, 154.4, 152.1, 148.8, 142.6, 134.5, 130.5, 130.0, 129.9, 127.1 (2C), 126.0, 117.0, 109.9, 72.1, 52.1, 50.1, 49.4, 49.2, 34.5, 27.5, 21.9, 21.4, 21.3. HRMS (ESI-TOF): m/z calcd for $C_{25}H_{26}N_3O_4$, 432.1923 found 432.1897 $[M+H]^+$.

General reaction procedure for the preparation of compounds 8f-h. Aldehyde (**1d**, 0.25 mmmol) and benzamide (**7a-c**, 0.25 mmol) were mixed in the presence of molecular sieves in ACN (1 mL) at rt. After 2h, a 10 mol% $Sc(OTf)_3$ was added, and stirring was continued at rt for another 10h. Next, the reaction mixture is stirred in a MW reactor at 70-100 °C for 1h. TLC showed the complete absence of starting materials and formation of new spots. Next, $Sc(OTf)_3$ (10 mol%) was added and the stirring was continued under MW at 100-150°C for 1.5h. After completion, ACN was removed, and the crude was purified by flash chromatography, using EtOAc in hexane as an eluent.

Methyl 2-(9-oxo-5-tosyl-5,6,7,9,14,14a-hexahydrobenzo[5,6][1,4]diazepino[7,1-*b*]quinazolin-7-yl)acetate (8f). White solid (66 mg, 54% yield, eluent: 31% EtOAc in hexane); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.83 (d, *J* = 7.5 Hz, 1H), 7.75 (d, *J* = 8.0 Hz, 2H), 7.45 – 7.33 (m, 3H), 7.22 (dd, *J* = 5.2, 3.7 Hz, 1H), 7.07 (dd, *J* = 5.5, 3.4 Hz, 2H), 6.94 – 6.81 (m, 3H), 6.18 (s, 1H), 5.58 (s, 1H), 5.04 (bs, 1H), 4.60 (d, *J* = 14.7 Hz, 1H), 3.74 (s, 3H), 3.41 – 3.29 (m, 2H), 2.97 (dd, *J* = 16.3, 7.1 Hz, 1H), 2.49 (s, 3H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 171.4, 161.7, 145.3, 144.3, 140.2, 138.8, 138.3, 134.3, 130.1, 129.5, 128.8, 127.9,

127.6, 126.7, 126.4, 119.5, 115.9, 114.5, 63.2, 52.2, 52.1, 46.8, 34.9, 21.8; HRMS (ESI-TOF): m/z calcd for $C_{26}H_{26}N_3O_5S$, 492.1593 found 492.1575 $[M+H]^+$.

Methyl 2-((7R,14aS)-11-methoxy-9-oxo-5-tosyl-5,6,7,9,14,14a-hexahydrobenzo[5,6][1,4]diazepino [7,1-*b*]quinazolin-7-yl)acetate (8g). White solid (75 mg, 58% yield, eluent: 36% EtOAc in hexane); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.74 (d, *J* = 8.3 Hz, 2H), 7.40 – 7.33 (m, 3H), 7.25 – 7.18 (m, 1H), 7.09 – 7.03 (m, 3H), 6.89 (d, *J* = 8.7 Hz, 1H), 6.86 – 6.79 (m, 1H), 6.15 (s, 1H), 5.58 (d, *J* = 2.3 Hz, 1H), 4.60 (dd, *J* = 14.8, 1.3 Hz, 1H), 3.78 (s, 3H), 3.74 (s, 3H), 3.39 – 3.29 (m, 2H), 3.02 (dd, *J* = 16.2, 7.6 Hz, 1H), 2.49 (s, 3H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 171.3, 161.5, 153.5, 144.2, 140.2, 138.9, 138.6, 138.2, 130.0, 128.6, 127.8, 127.5, 126.6 (2C), 123.0, 117.2, 117.0, 111.0, 63.2, 55.7, 52.1, 52.0, 46.9, 34.9, 21.6; HRMS (ESI-TOF): m/z calcd for $C_{27}H_{28}N_3O_6S$, 522.1698 found 522.1682 $[M+H]^+$.

Methyl 2-(11-chloro-9-oxo-5-tosyl-5,6,7,9,14,14a-hexahydrobenzo[5,6][1,4] diazepino[7,1-*b*]quinazolin-7-yl)acetate (8h). White solid (61 mg, 47% yield, eluent: 33% EtOAc in hexane); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.80 (d, *J* = 2.4 Hz, 1H), 7.74 (d, *J* = 8.3 Hz, 2H), 7.41 – 7.33 (m, 3H), 7.22 – 7.14 (m, 1H), 7.14 – 7.05 (m, 2H), 6.86 (d, *J* = 8.6 Hz, 1H), 6.84 – 6.80 (m, 1H), 6.20 (s, 1H), 5.54 (d, *J* = 2.9 Hz, 1H), 5.12 – 5.06 (m, 1H), 4.58 (dd, *J* = 14.9, 1.4 Hz, 1H), 3.73 (s, 3H), 3.36 – 3.30 (m, 2H), 2.99 (dd, *J* = 16.4, 7.4 Hz, 1H), 2.49 (s, 3H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 171.2, 160.7, 144.4, 143.8, 139.8, 138.8, 138.2, 134.3, 130.2, 129.0, 128.1, 127.6, 127.5, 126.8, 126.3, 124.7, 117.0, 116.0, 63.2, 52.3, 52.2, 47.1, 34.9, 21.8; LCMS (ESI): m/z 526 $[M+H]^+$.

Methyl (*E*)-4-(2-formyl-1H-indol-1-yl)but-2-enoate (9a).[16c] K_2CO_3 (2.2 mmol) at 0 °C was added to a solution of 1H-indole-2-carbaldehyde (2 mmol) in DMF (14 mL). After 30 min, a solution of methyl *trans*-4-bromo-2-butenoate (2.6 mmol) in DMF (14 mL) was added and stirring was continued at rt for 3h. After completion, reaction mixture was diluted with ethylacetate (100 mL) and washed with cold water (2 x 50 mL). The organic layer was separated, dried over Na_2SO_4 and concentrated under vacuum. The crude was purified on flash chromatography, using 17% EtOAc in hexane as an eluent to produce the title compound **9a**. Greenish solid (218 mg, 45% yield); ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.89 (s, 1H), 7.79 (d, *J* = 8.1 Hz, 1H), 7.47 – 7.42 (m, 1H), 7.38 – 7.28 (m, 2H), 7.26 – 7.21 (m, 1H), 7.14 – 7.07 (dt, *J* = 15.6, 4.6 Hz, 1H), 5.48 (td, *J* = 15.6, 1.9 Hz, 1H), 5.41 (dd, *J* = 4.6, 1.9 Hz, 2H), 3.69 (s, 3H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 182.6, 166.3, 143.3, 140.2, 135.0, 127.6, 126.6, 123.8, 121.7, 121.6, 118.6, 110.5, 51.7, 45.3; LCMS (ESI): m/z 244 $[M+H]^+$.

General reaction procedure for the preparation of compounds 10a-i. Sodium metabisulfite (0.375 mmol) in H_2O (0.5 mL) was added to a solution of aldehyde (**7**, 0.25 mmol) in ethanol (1 mL) at rt. After 30 min, *o*-phenylenediamine (**2**, 0.25 mmol) was added and stirring was continued at rt for another 6 h.

Then another half equivalent of sodium metabisulfite (0.125 mmol) in H_2O (0.5 mL) was added and the reaction was heated at 80 °C for 12 h. After completion, ethanol was removed, and the crude reaction mixture was diluted with EtOAc (15 mL) and treated with water (10 mL). The organic layer was dried over Na_2SO_4 and purified by flash chromatography, using EtOAc in hexane as an eluent.

Methyl 2-(6,7-dihydrobenzo[4',5']imidazo[2',1':3,4]pyrazino [1,2-*a*]indol-7-yl)acetate (10a). Yellowish solid (49 mg, 59% yield, eluent: 31% EtOAc in hexane); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.89 – 7.83 (m, 1H), 7.77 (d, *J* = 8.0 Hz, 1H), 7.48 – 7.43 (m, 2H), 7.41 (d, *J* = 8.2 Hz, 1H), 7.39 – 7.33 (m, 3H), 7.26 – 7.20 (m, 1H), 5.38 – 5.32 (m, 1H), 4.84 (d, *J* = 12.9 Hz, 1H), 4.45 (dd, *J* = 12.9, 4.1 Hz, 1H), 3.67 (s, 3H), 2.81 (dd, *J* = 16.6, 9.5 Hz, 1H), 2.71 (dd, *J* = 16.6, 3.9 Hz, 1H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 170.7, 144.0, 143.5, 137.7, 132.7, 128.7, 126.5, 124.0, 123.3, 122.3, 121.1, 120.0, 109.4, 109.0, 103.0, 52.24, 48.7, 43.9, 36.3; HRMS (ESI-TOF): m/z calcd for $C_{20}H_{18}N_3O_2$, 332.1399 found 332.1395 $[M+H]^+$.

Methyl 2-(10,11-dimethyl-6,7-dihydrobenzo[4',5']imidazo[2',1':3,4]pyrazino[1,2-*a*]indol-7-yl)acetate (10b). Off white solid (57 mg, 64% yield, eluent: 31% EtOAc in hexane); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.76 (d, *J* = 7.9 Hz, 1H), 7.61 (s, 1H), 7.42 – 7.32 (m, 3H), 7.28 (s, 1H), 7.25 – 7.19 (m, 2H), 5.32 – 5.25 (m, 1H), 4.82 (d, *J* = 12.9 Hz, 1H), 4.43 (dd, *J* = 12.8, 4.2 Hz, 1H), 3.70 (s, 3H), 2.80 (dd, *J* = 16.7, 9.8 Hz, 1H), 2.70 (dd, *J* = 16.6, 4.0 Hz, 1H), 2.45 (s, 3H), 2.42 (s, 3H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 170.8, 142.8, 142.7, 137.5, 132.7, 132.2, 131.2, 128.8, 127.0, 123.7, 122.1, 121.0, 120.1, 109.3, 109.1, 102.2, 52.2, 48.6, 43.8, 36.1, 20.6, 20.4; HRMS (ESI-TOF): m/z calcd for $C_{22}H_{22}N_3O_2$, 360.1712 found 360.1703 $[M+H]^+$.

Methyl 2-(10,11-dichloro-6,7-dihydrobenzo[4',5']imidazo[2',1':3,4]pyrazino[1,2-*a*]indol-7-yl)acetate (10c). Off white solid (58 mg, 58% yield yield, eluent: 32% EtOAc in hexane); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.91 (s, 1H), 7.78 (d, *J* = 8.0 Hz, 1H), 7.57 (s, 1H), 7.46 – 7.35 (m, 3H), 7.25 (dd, *J* = 10.4, 3.9 Hz, 1H), 5.31 – 5.26 (m, 1H), 4.84 (d, *J* = 13.0 Hz, 1H), 4.47 (dd, *J* = 12.9, 4.0 Hz, 1H), 3.70 (s, 3H), 2.83 (dd, *J* = 16.7, 9.2 Hz, 1H), 2.70 (dd, *J* = 16.7, 4.3 Hz, 1H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 170.5, 145.5, 143.8, 137.9, 132.2, 128.7, 127.5, 127.3, 125.9, 124.6, 122.6, 121.5, 121.2, 110.6, 109.5, 104.0, 52.5, 49.2, 44.0, 36.5; HRMS (ESI-TOF): m/z calcd for $C_{20}H_{16}Cl_2N_3O_2$, 400.0619 found 400.0608 $[M+H]^+$.

Methyl (*E*)-4-(5-chloro-2-formyl-3-methyl-1H-indol-1-yl)but-2-enoate (9b). K_2CO_3 (2.2 mmol) at 0 °C was added to a solution of 5-chloro-3-methyl-1H-indole-2-carbaldehyde (2 mmol) in DMF (14 mL). After 30 min, a solution of methyl *trans*-4-bromo-2-butenoate (2.6 mmol) in DMF (14 mL) was added and stirring was continued at rt for 4h. After completion, reaction mixture was diluted with ethylacetate (100 mL) and washed with cold water (2 x 50 mL). The organic layer was separated, dried over Na_2SO_4 and concentrated under vacuum. The crude was purified on flash chromatography, using 19% EtOAc in hexane

as an eluent to produce the title compound **9b**. Yellowish solid (238 mg, 41% yield); ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.14 (s, 1H), 7.70 (d, *J* = 1.8 Hz, 1H), 7.37 (dd, *J* = 8.9, 1.9 Hz, 1H), 7.19 (d, *J* = 8.9 Hz, 1H), 7.05 (dt, *J* = 15.6, 4.5 Hz, 1H), 5.42 (dt, *J* = 15.6, 1.9 Hz, 1H), 5.34 (dd, *J* = 4.5, 1.8 Hz, 2H), 3.68 (s, 3H), 2.63 (s, 3H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 181.3, 166.2, 143.4, 137.4, 131.2, 128.3, 128.1, 126.6, 127.0, 121.6, 120.9, 111.5, 51.7, 45.3, 8.6; LCMS (ESI): m/z 292 $[M+H]^+$.

Methyl 2-(2-chloro-14-methyl-6,7-dihydrobenzo[4',5']imidazo[2',1':3,4] pyrazino[1,2-*a*]indol-7-yl)acetate (10d). Off white solid (60 mg, 64% yield, eluent: 29% EtOAc in hexane); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.93 (d, *J* = 5.9 Hz, 1H), 7.68 (d, *J* = 1.3 Hz, 1H), 7.52 – 7.44 (m, 1H), 7.42 – 7.25 (m, 5H), 5.42 – 5.28 (m, 1H), 4.76 (d, *J* = 12.8 Hz, 1H), 4.50 – 4.36 (m, 1H), 3.68 (s, 3H), 2.90 – 2.64 (m, 5H); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 170.8, 143.7, 135.7, 132.2, 130.4, 126.3, 124.7, 123.6, 123.5, 120.1, 119.9, 110.3, 109.0, 52.4, 48.8, 44.1, 36.3, 9.9; LCMS (ESI): m/z 380 $[M+H]^+$.

Methyl 2-(2-chloro-10,11,14-trimethyl-6,7-dihydrobenzo[4',5']imidazo [2',1':3,4]pyrazino[1,2-*a*]indol-7-yl)acetate (10e). Off white solid (69 mg, 68% yield, eluent: 30% EtOAc in hexane); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.66 (s, 1H), 7.28 – 7.23 (m, 2H), 7.19 (s, 1H), 5.28 – 5.22 (m, 1H), 4.73 (d, *J* = 12.6 Hz, 1H), 4.36 (dd, *J* = 12.8, 3.9 Hz, 1H), 3.70 (s, 1H), 2.77 (dd, *J* = 16.6, 9.7 Hz, 1H), 2.69 (dd, *J* = 15.9, 4.2 Hz, 1H), 2.45 (s, 1H), 2.42 (s, 2H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 170.8, 143.1, 135.4, 132.6, 132.0, 130.7, 130.3, 125.9, 124.5, 124.1, 120.3, 119.5, 113.5, 110.1, 108.9, 52.2, 48.5, 43.9, 36.1, 20.6, 20.4, 9.7; HRMS (ESI-TOF): m/z calcd for $C_{23}H_{23}ClN_3O_2$, 408.1478 found 408.1477 $[M+H]^+$.

Methyl 2-(2,10,11-trichloro-14-methyl-6,7-dihydrobenzo[4',5']imidazo [2',1':3,4]pyrazino[1,2-*a*]indol-7-yl)acetate (10f). Off white solid (55 mg, 49% yield, eluent: 30% EtOAc in hexane); ^{1}H NMR (500 MHz, Acetone-d_6) δ 7.94 (s, 1H), 7.89 (s, 1H), 7.72 (d, *J* = 1.9 Hz, 1H), 7.57 (d, *J* = 8.7 Hz, 1H), 7.32 (dd, *J* = 8.7, 2.0 Hz, 1H), 5.68 – 5.59 (m, 1H), 5.05 (dd, *J* = 13.1, 0.9 Hz, 1H), 4.57 (dd, *J* = 13.1, 4.2 Hz, 1H), 3.52 (s, 3H), 2.94 (dd, *J* = 16.1, 7.6 Hz, 1H), 2.83 – 2.74 (m, 6H); ^{13}C{^{1}H} NMR (125 MHz, Acetone-d_6) δ 171.1, 146.9, 144.9, 136.8, 133.5, 130.8, 126.5, 126.3, 125.1, 124.8, 121.1, 120.1, 114.9, 112.8, 112.3, 55.0, 52.1, 50.2, 44.9, 37.4, 9.7; HRMS (ESI-TOF): m/z calcd for $C_{21}H_{17}Cl_3N_3O_2$, 448.0386 found 448.0380 $[M+H]^+$.

Methyl (*E*)-4-(2-formyl-1H-pyrrol-1-yl)but-2-enoate (9c). K_2CO_3 (2.2 mmol) at 0 °C was added to a solution of 1H-pyrrole-2-carbaldehyde (2 mmol) in DMF (14 mL). After 30 min, a solution of methyl *trans*-4-bromo-2-butenoate (2.6 mmol) in DMF (14 mL) was added and stirring was continued at rt for 3h. After completion, reaction mixture was diluted with ethylacetate (100 mL) and washed with cold water (2 x 50 mL). The organic layer was separated, dried over Na_2SO_4 and concentrated under vacuum. The crude was purified on flash chromatography, using 12% EtOAc in hexane as an eluent to produce the

title compound **9c**. Yellowish solid (213 mg, 55% yield); ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.56 (s, 1H), 7.05 (dt, *J* = 15.6, 4.8 Hz, 1H), 7.00 (dd, *J* = 4.0, 1.7 Hz, 1H), 6.96 – 6.92 (m, 1H), 6.32 (dd, *J* = 4.0, 2.5 Hz, 1H), 5.55 (dt, *J* = 15.6, 1.9 Hz, 1H), 5.16 (dd, *J* = 4.8, 1.9 Hz, 2H), 3.72 (s, 3H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 179.5, 166.3, 143.8, 131.3, 125.0, 121.9, 110.6, 51.8, 49.3; LCMS (ESI): m/z 194 $[M+H]^+$.

Methyl 2-(5,6-dihydrobenzo[4,5]imidazo[1,2-*a*]pyrrolo[2,1-*c*]pyrazin-6-yl)acetate (10g). Off white solid (39 mg, 56% yield yield, eluent: 32% EtOAc in hexane); ^{1}H NMR (500 MHz, Acetone-d_6) δ 7.63 – 7.56 (m, 1H), 7.55 – 7.49 (m, 1H), 7.26 – 7.18 (m, 2H), 7.05 (dd, *J* = 2.2, 1.4 Hz, 1H), 6.90 – 6.83 (m, 1H), 6.31 (dd, *J* = 3.6, 2.7 Hz, 1H), 5.44 – 5.35 (m, 1H), 4.70 (d, *J* = 13.3 Hz, 1H), 4.62 – 4.55 (m, 1H), 3.55 (s, 3H), 2.76 (dd, *J* = 15.8, 8.1 Hz, 1H), 2.66 (d, *J* = 5.6 Hz, 1H); ^{13}C{^{1}H} NMR (125 MHz, Acetone-d_6) δ 170.2, 144.6, 144.0, 133.2, 123.9, 121.9, 121.8, 121.7, 118.9, 109.6, 109.4, 108.8, 51.2, 48.8, 47.3, 36.3; HRMS (ESI-TOF): m/z calcd for $C_{16}H_{16}N_3O_2$, 282.1242 found 282.1240 $[M+H]^+$.

Methyl 2-(9,10-dimethyl-5,6-dihydrobenzo[4,5]imidazo[1,2-*a*]pyrrolo [2,1-*c*]pyrazin-6-yl)acetate (10h). Off white solid (47 mg, 61% yield, eluent: 35% EtOAc in hexane); ^{1}H NMR (500 MHz, Acetone-d_6) δ 7.38 (s, 1H), 7.28 (s, 1H), 7.01 (dd, *J* = 2.4, 1.5 Hz, 1H), 6.80 (dd, *J* = 3.7, 1.3 Hz, 1H), 6.28 (dd, *J* = 3.6, 2.7 Hz, 1H), 5.36 – 5.25 (m, 1H), 4.66 (d, *J* = 13.3 Hz, 1H), 4.54 (dd, *J* = 13.3, 4.4 Hz, 1H), 3.57 (s, 3H), 2.72 (dd, *J* = 15.8, 8.4 Hz, 1H), 2.62 (dd, *J* = 15.8, 5.5 Hz, 1H), 2.38 (s, 3H), 2.35 (s, 3H); ^{13}C{^{1}H} NMR (125 MHz, Acetone-d_6) δ 171.1, 144.1, 132.5, 131.5, 131.3, 124.4, 123.0, 120.1, 110.5, 110.4, 109.1, 52.1, 49.6, 48.1, 37.0, 30.3, 20.4, 20.3; HRMS (ESI-TOF): m/z calcd for $C_{18}H_{20}N_3O_2$, 310.1555 found 310.1556 $[M+H]^+$.

Methyl 2-(9,10-dichloro-5,6-dihydrobenzo[4,5]imidazo[1,2-*a*] pyrrolo[2,1-*c*]pyrazin-6-yl)acetate (10i). Off white solid (48 mg, 56% yield, eluent: 35% EtOAc in hexane); ^{1}H NMR (500 MHz, Acetone-d_6) δ 7.81 (s, 1H), 7.74 (s, 1H), 7.11 (dd, *J* = 2.4, 1.5 Hz, 1H), 6.91 (dd, *J* = 3.7, 1.3 Hz, 1H), 6.33 (dd, *J* = 3.7, 2.6 Hz, 1H), 5.53 – 5.41 (m, 1H), 4.74 (dd, *J* = 13.4, 0.9 Hz, 1H), 4.61 (dd, *J* = 13.4, 4.4 Hz, 1H), 3.56 (s, 3H), 2.82 – 2.76 (m, 2H), 2.71 (dd, *J* = 16.1, 5.9 Hz, 1H); ^{13}C{^{1}H} NMR (125 MHz, Acetone-d_6) δ 171.0, 147.1, 145.1, 133.8, 125.9, 125.7, 125.4, 121.9, 120.5, 112.3, 110.9, 110.8, 52.1, 50.0, 48.1, 37.0; HRMS (ESI-TOF): m/z calcd for $C_{16}H_{14}Cl_2N_3O_2$, 350.0463 found 350.0461 $[M+H]^+$.

Methyl 2-(8,9-dihydro-2H-indolo[2',1':3,4]pyrazino[1,2-*a*]quinazolin-8-yl) acetate (12). Sodium bisulfite (0.25 mmol) in H_2O (0.5 mL) was added to a solution of aldehyde (**9**, 0.25 mmol) in ethanol (1 mL) at rt. After 30 min, 2-aminobenzylamine (**11**, 0.25 mmol) was added and stirring was continued at rt for another 6 h. Then another half equivalent of sodium bisulfite (0.125 mmol) in H_2O (0.5 mL) was added and the reaction was heated at 80 °C for 12 h. After completion, ethanol was removed, and the crude reaction mixture was diluted with EtOAc (15 mL) and extracted with 10 mL water. The organic layer was dried over

Na_2SO_4 and purified on flash chromatography, using 45 % EtOAc in hexane as an eluent. Yellowish solid (38 mg, 45% yield); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.70 (d, *J* = 8.0 Hz, 1H), 7.40 (s, 1H), 7.30 – 7.25 (m, 2H), 7.25 – 7.17 (m, 2H), 7.17 – 7.12 (m, 1H), 7.01 (t, *J* = 7.4 Hz, 1H), 6.92 (d, *J* = 7.4 Hz, 1H), 4.75 (q, *J* = 13.2 Hz, 2H), 4.46 (dd, *J* = 12.6, 1.2 Hz, 1H), 4.32 (dd, *J* = 12.6, 3.5 Hz, 1H), 4.04 – 3.97 (m, 1H), 3.64 (s, 3H), 2.73 (dd, *J* = 16.6, 3.6 Hz, 1H), 2.53 (dd, *J* = 16.6, 9.3 Hz, 1H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 171.3, 146.7, 137.1, 128.6, 128.0, 125.2, 124.8, 124.4, 123.9, 122.3, 120.8, 120.4, 109.1, 104.5, 54.4, 52.1, 48.9, 43.4, 33.7; HRMS (ESI-TOF): m/z calcd for $C_{21}H_{20}N_3O_2$, 346.1555 found 346.1554 $[M+H]^+$.

Methyl 2-(9-oxo-6,7-dihydro-9H-indolo[2',1':3,4]pyrazino[2,1-*b*]quinazolin-7-yl)acetate (13). Oxone (0.1 mmol) was added to a solution of compound **12** (0.1 mmol) in DMF:water (2:1) mL and stirring continued at rt. After 6h, another one equivalent of oxone (0.1 mmol) was added and stirred for another 6h. After completion, reaction mixture was diluted with ethylacetate (25 mL) and washed with cold water (2 x 10 mL). The organic layer was dried over Na_2SO_4 and purified on flash chromatography, using 25 % EtOAc in hexane as an eluent. Off white solid (30 mg, 85% yield); ^{1}H NMR (500 MHz, Acetone-d_6) δ 8.27 – 8.22 (m, 1H), 7.87 – 7.82 (m, 1H), 7.77 (dd, *J* = 8.0, 0.8 Hz, 1H), 7.72 (dd, *J* = 8.0, 0.5 Hz, 1H), 7.59 (dd, *J* = 8.4, 0.8 Hz, 1H), 7.55 – 7.49 (m, 2H), 7.39 – 7.34 (m, 1H), 7.22 – 7.17 (m, 1H), 5.92 – 5.86 (m, 1H), 4.97 (dd, *J* = 13.3, 1.1 Hz, 1H), 4.54 (dd, *J* = 13.3, 4.0 Hz, 1H), 3.56 (s, 3H), 2.73 – 2.69 (m, 2H); ^{13}C{^{1}H} NMR (125 MHz, Acetone-d_6) δ 171.1, 160.9, 149.1, 145.1, 138.5, 135.3, 129.6, 129.1, 128.1, 127.5, 127.1, 125.2, 122.9, 121.8, 121.6, 110.9, 105.8, 52.1, 48.3, 43.4, 36.1; LCMS (ESI): m/z 360 $[M+H]^+$.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available for free of Charge on the ACS Publications website at: DOI: X-ray diffraction data and copies of NMR spectra (PDF).

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Notes

The authors declare no competing financial interest.

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