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Metal Free Activation of C(SP³)-H Bond, Practical and Rapid Synthesis of Privileged 1-Substituted-1,2,3,4-Tetrahydroisoquinolines

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Dedication: To my Beloved Father, who passed away recently

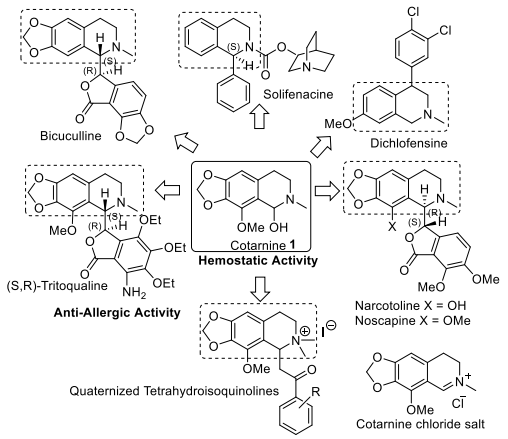
Abstract: The reaction of cotarnine and acyl/aryl ketones in green solvents provides an efficient approach to an array of privileged 1,2,3,4-tetrahydroisoquinolines in excellent yields by metal free Activaion of C(SP^3)-H bonds. This one-pot procedure takes place under base-free conditions at room temperature, and tolerates a wide range of functionalities. The reaction is highly chemo-selective, scalable in multi-gram scale, and pure products were isolated by simple filtration without work-up. Interestingly, the complementary two-step procedure from cotarnine halide salts gives the Mannich products in good yields. The scope was elaborated to 9-bromocotarnine salts to access 9-bromonoscapine-inspired diverse analogues. The methodology is developed based upon structural similarity of cotarnine derivatives with noscapinoids which represent an emerging class of microtubule-modulating anticancer agents.

Introduction

Members of the privileged tetrahydroisoquinoline family of alkaloids display a wide range of biological properties such as antitumor and antimicrobial activities.[1] Of particular significance within this family is the anti-tussive drug *(S,R)*-noscapine and analogues which display anti-tumor activity by impairing tubulin polymerization without severe side effects.[1,2] Noscapine causes mitotic arrest of tumor cells, induces apoptosis of tumor cells in vivo, and is in phase I/phase II clinical trials for multiple myeloma.[3] The core unit of noscapine known as cotarnine, an oxidative degradation product of the drug, is a crystalline alkaloid which is available chiefly in salt form (Scheme 1).[4a] Cotarnine hydrochloride is known to have hemostatic activity.[4b] Additionally, cotarnine is the key component of tritoqualin (inhibostamin®) which is used as an anti-allergic drug,[5] and has preventive effect on liver injury in rats induced by treatment with CCl_4.[6] Hence, derivatization of cotarnine could pave the way to simplified noscapine analogues as potential anticancer agents.[7]

It is noteworthy that the synthesis of 2-methyl-1-(2-oxo-aryl)-1,2,3,4-tetrahydroisoquinolines and their biological applications have been scarcely documented in literature.[8] Importantly, quaternized tetrahydroisoquinolines were synthesized, from cotarnine iminium methylsulfate (prepared in multiple steps from 3,4,5-trihydroxybenzoic acid), and their biological activities were investigated (Scheme 1).[9]

Thus, various biological activities have been found such as filamin α-binding anti-inflammatory analgesic,[9a] inhibition of tau phosphorylation,[9b] and inhibition of growth of cancer cells.[9c] Importantly, green chemistry is becoming a high priority in fine chemicals and pharmaceutical industries in an effort to reduce waste, reduce costs and develop environmentally benign processes.[10] Indeed, chemical synthesis from laboratory to industrial level differs in respect to reaction scale, reproducibility of methodology, product purity, atom economy, cost and *E*-factor of the process.[11]



Scheme 1. 1,2,3,4-Tetrahydroisoquinoline Scaffold as a Privileged Structure in Drug Discovery.Scheme Caption.

As part of our goal of research aimed to develop environmentally benign methods[12] for carbon-carbon bond-formation for use in medicinal chemistry and development of novel anti-cancer agents,[27] herein, we wish to report an efficient one-pot synthesis of 1-substituted-1,2,3,4-tetrahydro isoquinolines involving cotarnine and a diverse array of ketones in green solvents at room temperature under base-free-conditions to give simplified noscapine analogues in excellent yields. This reaction is scalable to multi-gram scale and

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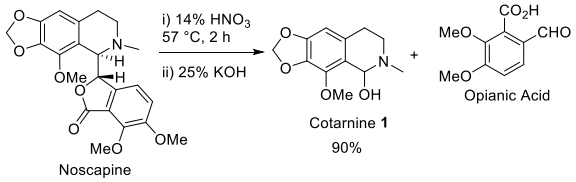
provides products by a non-chromatographic method (precipitation in the reaction mixture). In this context, we also investigated the complementary approach for preparation of 1-substituted-1,2,3,4-tetrahydroisoquinolines through a two-step procedure from cotarnine halide salts. The approach is elaborated to 9-bromo cotarnine derivatives to access structural diverse scaffolds for biological evaluation.

Results and Discussion

The main core unit cotarnine **1** could be synthesized in gram scale by oxidative degradation of commercially available (*S,R*)-noscapine with 14% HNO_3 (Scheme 2) along with opianic acid in 90% yield.[13,14]

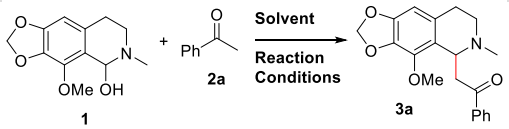


Scheme 2. Synthesis of Cotarnine 1 from (S,R) Noscapine.[13,14]

We first studied the reactivity of cotarnine **1** with acetophenone **2a** as model substrate (Table 1). Initial attempt using 1-5 equiv. of various inorganic bases[8b] such as $NaHCO_3$/ K_2CO_3/Na_2CO_3/ KOH/ NaOH afforded only low yields of the desired coupling product **3a** (15-30%) in methanol at 55-70°C after 5-48 h (entry 1). Further investigation of this reaction under microwave at 55-70 °C afforded **3a** in 55-70% yields for 1 h but with mixture of by-products (entry 2).[8j-k,14,15] In the absence of base, the microwave reaction gave **3a** in low yield (55 °C, <30%, entry 3), while the reaction by classical heating proceeded well (80%, entry 4) at the same temperature.

Further close investigation revealed that the reaction could be performed in high yield (92%) in methanol at ambient temperature without use of any base (entry 5). In addition, we were pleased to see that the formed product separated itself progressively from the reaction medium and could be collected just by simple filtration as white solid with high purity. Aprotic polar solvents such as CH_2Cl_2 and CH_3CN were found ineffective (entries 6 and 7) for this reaction compared with protic polar solvents.

Table 1: Optimization Reaction Conditions for Coupling of Cotarnine **1** with **2a**

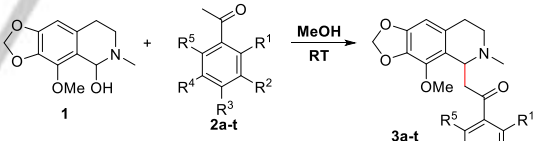


Entry[a, d]	Solvent	Temp.	Time (h)	Yield* (%) **3a**[b]
1[c]	MeOH	55-70 °C	5-48	<15-30
2[c]	MeOH	55-70°C, MW	1	<55-70
3	MeOH	55 °C, MW	1	<30
4	MeOH	55 °C	0.7	80
5	MeOH	25 °C	0.5	92
6	CH_2Cl_2	25 °C	2	<5
7	CH_3CN	25 °C	2	<15
8	H_2O	25 °C	2	80
9	EtOH	25 °C	1	91
10	80% MeOH	25 °C	1	91
11	50% MeOH	25 °C	1	88
12	30% MeOH	25 °C	1	85

[a]**1** (2 mmol) and **2a** (2 mmol) were dissolved in 1 ml of solvent for indicated time. [b]Isolated yields. [c]$NaHCO_3$/K_2CO_3/ Na_2CO_3/ KOH/NaOH used for entry 1 and 2. [d]Base-free condition was used for entries 3-12. *Coupling reaction: **3a** collected by simple filtration.

Methanol and ethanol were found equally good (entry 5 vs entry 9) while water afforded a comparable yield (80%) but with a longer reaction time (entry 8). Aqueous methanol afforded also a comparable yield (entry 10) but the solubility issue of acetophenone became problematic when increasing the percentage of water (entries 11 and 12), which would limit its use for broad range of substrates. So methanol/ethanol and 80% methanol are the solvents of choice for a variety of syntheses.

The procedure was amenable to multi-gram scale synthesis on 20 mmol scale reaction to give **3a** in >90% yield without any side-product formation. The latter was isolated as described above by simple filtration without further flash chromatography. With optimized conditions in our hand, we studied the scope of this methodology with a broad range of acetophenones **2a-2t** and **2aa-2aq**. In all cases, the reaction was successful to give **3a-3t** and **3aa-3aq**, respectively (Schemes 2, 3, and 5) in high yields.



3a R^1 = H, R^2 = H, R^3 = H, R^4 = H, R^5 = H, 92%
3b R^1 = H, R^2 = H, R^3 = **Cl**, R^4 = H, R^5 = H, 92%
3c R^1 = H, R^2 = H, R^3 = **Br**, R^4 = H, R^5 = H, 88%
3d R^1 = H, R^2 = H, R^3 = **OH**, R^4 = H, R^5 = H, 90%
3e R^1 = H, R^2 = H, R^3 = **NH_2**, R^4 = H, R^5 = H, 92%
3f R^1 = H, R^2 = H, R^3 = **NO_2**, R^4 = H, R^5 = H, 90%
3g R^1 = **OH**, R^2 = H, R^3 = H, R^4 = H, R^5 = H, 89%
3h R^1 = **Me**, R^2 = H, R^3 = H, R^4 = H, R^5 = H, 90%
3i R^1 = **NH_2**, R^2 = H, R^3 = H, R^4 = H, R^5 = H, 92%
3j R^1 = H, R^2 = **NO_2**, R^3 = H, R^4 = H, R^5 = H, 90%
3k R^1 = H, R^2 = **OMe**, R^3 = H, R^4 = H, R^5 = H, 91%
3l R^1 = H, R^2 = **NH_2**, R^3 = H, R^4 = H, R^5 = H, 93%
3m R^1 = **OH**, R^2 = H, R^3 = H, R^4 = **Br**, R^5 = H, 93%
3n R^1 = **Cl**, R^2 = H, R^3 = **Cl**, R^4 = H, R^5 = H, 91%
3o R^1 = **Cl**, R^2 = H, R^3 = H, R^4 = **Cl**, R^5 = H, 91%
3p R^1 = H, R^2 = H, R^3 = **Cl**, R^4 = **Cl**, R^5 = H, 89%
3q R^1 = **OMe**, R^2 = H, R^3 = **OMe**, R^4 = **Cl**, R^5 = H, 93%
3r R^1 = **OH**, R^2 = **Me**, R^3 = **NO_2**, R^4 = H, R^5 = H, 90%
3s R^1 = **OMe**, R^2 = H, R^3 = **OMe**, R^4 = Me, R^5 = H, 93%
3t R^1 = **OMe**, R^2 = H, R^3 = **OMe**, R^4 = H, R^5 = **OMe**, 94%

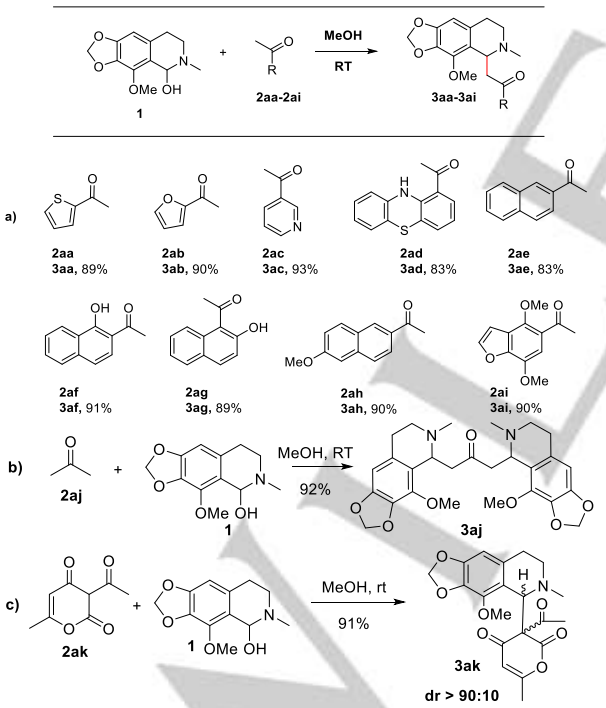
Products collected by simple filtration

Before adding MeOH **After adding MeOH** **After stirring 15 min in MeOH**

Formation of product 3a

Scheme 3. Reaction of Ortho-, Meta- and Para-Substituted Acetophenones with Cotarnine 1.

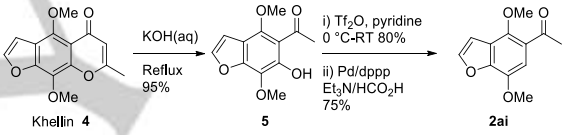
Acetophenones containing halogen group at *para*-position such as *p*-chloro (**2b**) and *p*-bromo (**2c**) reacted efficiently with cotarnine in 92% (**3b**) and 88% (**3c**) yields, respectively, as white crystalline solids (Scheme 2). Similarly, electron-donating groups such as *p*-hydroxy (**2d**) and *p*-amino (**2e**) in the acetophenone ring afforded the corresponding products as white and grey solids **3d** and **3e**, respectively, with high yields (90-92%) in contrast to *p*-nitro (**2f**) which was collected as yellow solid **3f** in 90% yield. It is noteworthy that, in case of *p*-hydroxy and *p*-amino acetophenones highly chemoselective C-C cross coupling (nucleophilic addition) is preferred over products resulting from the reactivities of phenol and aniline (aromatic substitution). The acetophenones containing hydroxyl-, methyl-, and amino-, groups in *ortho*-position (**2g-2i**) led to the substituted products **3g-3i** in 89-92% yields (Scheme 3). The *meta*-substituted electron donating groups such as *m*-methoxy (**2k**) and *m*-amino (**2l**) gave the desired coupling products (**3k, 3l**) in a highly chemoselective manner (91-93% yields). The effect of the electron-withdrawing *m*-nitro group (**2j**) was also positive giving rise to **3j** as yellow solid (90%) under similar reaction conditions (45 min). All the products were isolated with high yield with a minimum of three-time reproducibility in order to confirm validity of our data even in multi-gram scale. Few of these products being slightly soluble in methanol, it was therefore necessary to cool the reaction under ice for 5 min before filtering, and subsequent washing with 1 ml of cold methanol was performed to maximize the yield.



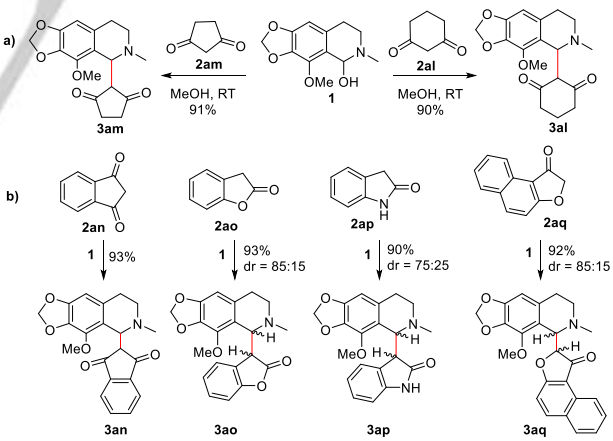
Scheme 4. (a) Reactivity of Heteroaromatic, Naphthyl and Benzofuran Backbones (3aa-3ai are the corresponding product yields of acetophenones 2aa-2ai). (b) Selectivity with Excess Acetone. (c) Selectivity of Dehydroacetic Acids 2ak with Cotarnine 1.

Di- and tri-substituted substrates were next investigated in order to get insight into the electronic and steric effects on reactivity (Scheme 3). Di-substituted substrates such as 2,5-dichloro (**2o**), 2,4-dichloro (**2n**), and 4,5-dichloro (**2p**) acetophenones proceeded with high yield with 0.5-1 h reaction time. The 2-hydroxy-5-bromo functionality (**2m**) afforded 93% of white solid within 30 min. Acetophenones such as 2,4-dimethoxy-5-chloro (**2q**), 2,4-dimethoxy-5-methyl (**2s**), and 2-hydroxy-3-methyl-4-nitro (**2r**) acetophenones generated the coupling products with cotarnine **1** in high yields without any side product. Highly electron-donating 2,4,6-trimethoxy-acetophenone (**2t**) also reacted smoothly to furnish white solids in 93% yield.

In addition to aromatic acetophenones, a range of hetero-aromatic acetophenones were examined subsequently (Scheme 4a). Substrates such as 2-acetyl thiophene (**2aa**) and 2-acetyl furan (**2ab**) were successfully reacted with cotarnine **1** affording white solid products in 89 and 90% yield after 30-45 minutes. Similarly, 3-acetyl pyridine (**2ac**) reacted efficiently to produce the desired product **3ac** in 93% yield without any side products. A tricyclic heteroaromatic compound such as 2-acetyl phenothiazine (**2ad**) afforded 83% of the desired chemoselective coupling product **3ad** as orange solid without any competing reactions due to the presence of *N*- and *S*- heteroatoms.



Scheme 5. Synthesis of Acetophenone 2ai from Khellin.



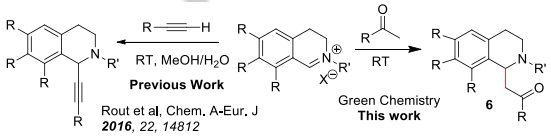
Scheme 6. a) Reaction of Cotarnine 1 with 1,3-Cyclohexadione and 1,3-Cyclopentadione. b) Reaction of Cotarnine with Indane 1,3-dione and Heterocyclic Compounds.

Next, we drew our attention to 2-acetyl naphthalenes. Thus, substrates such as 1-acetyl naphthalene **(2ae**), 2-acetyl naphthol-1 (**2af**), 1-acetyl naphthol-2 (**2ag**) and 6-methoxy 2-acetyl naphthalene (**2ah**) were subjected to reaction under similar conditions (Scheme 4a). Again, the reaction was highly

chemoselective and proceeded in high yields to give **3ae-ah** (89-91% yields). The reactivity of 1-(4,7-dimethoxybenzofuran-5-yl)ethanone **2ai** was also investigated. The latter was synthesized by treatment of the commercially available khellin **4** with KOH under reflux condition.[16] Further treatment with triflic anhydride and subsequent treatment with Pd/dppp of **5** afforded **2ai** in 75% yield (Scheme 5, See Supp. info). Gratifyingly, this substrate also reacted efficiently at room temperature to give **3ai** in 90% yield as white needles. Next, with acetone **2aj** (in excess) the *bis*-condensation product **3aj** was formed in high yield (Scheme 4b). Finally, dehydroacetic acid **2ak** existing as the enol form[17] in solution, namely 3-acetyl-4-hydroxy-6-methyl-2H-pyran-2-one, generated compound **3ak** in high yield and high diastereoselectivity (91%, dr > 90:10), as white solid (Scheme 4c).

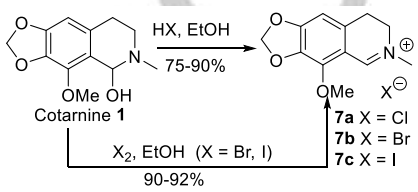
1,3-Diones were also investigated such as 1,3-cyclohexanedione **2al**, cyclopentane-1,3-dione **2am** (Scheme 6a), and 2H- indene-1,3-dione (**2an**) (Scheme 6b) leading to **3al-3an** in >90% yields It should be noted that products **3am** and **3al** have very low solubility with most of the solvents. To the best of our knowledge, the synthesis of close noscapine analogues based on the isomers of position relative to the phthalide moiety (1,3-dihydro-2-benzofuran-1-one) has not been reported so far. Hence, a modest diastereoselectivity was observed, when benzofuran-2(3H)-one **2ao** and naphtha [2,1-b]furan-1(2H)-one **2aq** were efficiently coupled to cotarnine **1** to provide **3ao** and **3aq** as inseparable mixture of diastereoisomers (*dr* = 85:15, determined by ^{1}H NMR) in good yields. NOESY studies (400 MHz) on **3aq** were not conclusive to assign the stereochemical relationship. Replacing the lactone by the lactam function as exemplified by indolin-3-one **2ap** gave access to a very close synthetic precursor **3ap** (90%, inseparable *dr* = 75:25) of alkaloid narceine imide (Scheme 6b).[15] Diastereomeric relationship of product **3ak, 3ao, 3ap** and **3aq** were determined by energy minimized structure by Discover module and the Cff91 force-field of the Insight II package by measuring H-C-C-H dihedral angles (Accelrys, Inc).(Please see Supp info)

To the best of our knowledge, there is no report [18, 19] on the addition of acylketone enolates[27] to cotarnine halide salts. However, Yamato and co-workers[8i] reported a related method based on *N,O*-acetal-derived tetrahydroisoquinolines starting from iminium bromide. As a complementary approach to the one-pot procedure from cotarnine (Schemes 3 and 4), we investigated the two-step procedure for the synthesis of functionalized 1,2,3,4-tetrahydroisoquinolines **6** from these iminium salts and various aromatic and hetero-aromatic ketones under basic reaction conditions (Scheme 7). Importantly, the isoquinoline iminiums salts are key synthetic intermediates to get access to chiral isoquinoline-derived alkaloids as reported by Schreiber and Taylor[20] for diversity-oriented synthesis (DOS).



Scheme 7. Synthesis of Tetrahydroisoquinolines from Isoquinoline Iminiums halides.

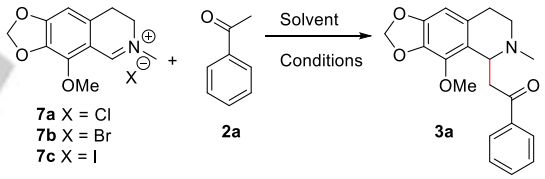
Cotarnine could easily be converted to its stable salts **7a**-**7c** by reaction with dilute hydrohalic acids (HCl, HBr, HI) in ethanol in 75-90% yields. It should be noted that Stephenson and co-workers[21] have recently reported the synthesis of diverse 1-substituted tetrahydroisoquinolines from iminium bromides generated *in situ* using visible light, and a broad range of nucleophile (methallyl trimethylsilane, silylenol ethers, and 1,3-dicarbonyls).



Scheme 8. Methods for Synthesizing Cotarnine Halide Salts.

Alternatively, cotarnine bromide and iodide salts could also be synthesized in 90-92% yields by direct addition of the respective molecular halogen (Br_2, I_2) and cotarnine in ethanol at room temperature (Scheme 8).

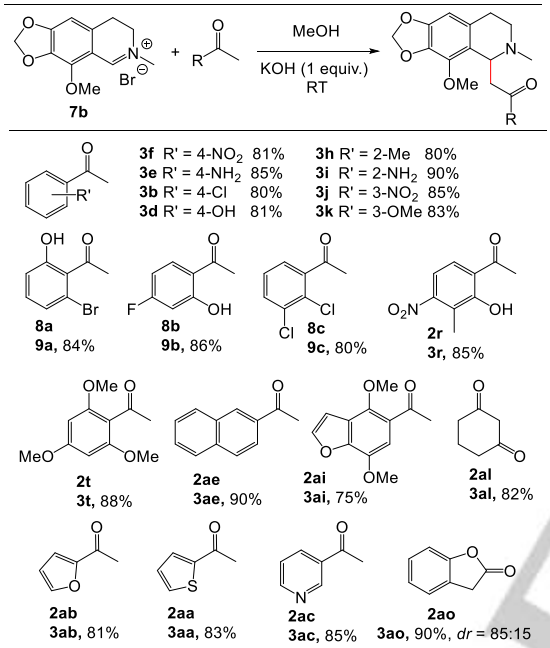
Table 2. Optimization Reaction Conditions for Coupling iminium salts 7a-7c with Acetophenone 2a



Entry[a]	Solvent	Temp.	Time (h)	Yield*(%) of **3a**[b]
1[c]	MeOH	RT	48	0
2[c]	MeOH	55 °C	24	0
3[d]	MeOH	RT	2	<5
4[e]	MeOH	RT	2	30
5[f]	MeOH	RT	0.5	87
6[g]	MeOH	RT	0.5	85
7[h]	MeOH	RT	0.5	83
8[f]	CH_2Cl_2	RT	2	<5
9[f]	CH_3CN	RT	2	<5
10[f]	H_2O	RT	4	75
11[f]	EtOH	RT	1	65
12[f]	50% MeOH	RT	1	73

[a]Cotarnine bromide salt **7b** (2 mmol), acetopheneone **2a** (2 mmol), and KOH (2 mmol) were dissolved in 0.5 ml of solvent for indicated time. [b]Isolated yields. [c]No base. [d]K_2CO_3/ Na_2CO_3. [e]NaOH. [f]KOH (entries 5-12). *The product was collected by simple filtration. [g]Cotarnine iodide salt **7c**. [h]Cotarnine chloride salt **7a**.

With cotarnine salts 7a-7c in hand for C-C bond formation, we investigated the reactivity of bromide salts 7b with acetophenone 2a in 1:1 ratio (Table 2). The reaction did not proceed in the absence of base in methanol at room temperature, even after prolonging heating at 55 °C (24-48 h) (entries 1 and 2). Use of carbonate bases was less successful, as Na2CO3 and K2CO3 gave the coupling product 3a in very low yield (entry 3). The use of the strong base NaOH (1 equiv.) did allow to improve the coupling efficiency in a significant way (entry 4). In contrast, KOH (1 equiv.) performed well leading to 6b in 87% yield (entry 5). After 20-45 min, the white solid product was easily separated from the reaction mixture by simple filtration, washed with MeOH, and dried.



Scheme 9. Reaction of Various Ketones with 7b.

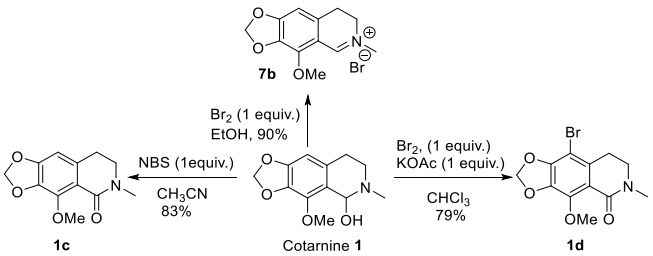
Among the solvents studied, polar protic solvents such as CH3OH was found to be the most effective choice over C2H5OH and H2O (entries 5-7 vs entries 10 and 11) or mixture of solvents (entry 12), whereas polar aprotic solvents such as CH2Cl2 and CH3CN did not afford any product (entries 8 and 9). Cotarnine iodide salt 7c and cotarnine chloride 7a were also engaged in the C-C bond formation process leading to 3a in the same range of yields (85% and 83%, respectively) (entries 6 and 7).

In order to explore the scope of the reaction, cotarnine bromide salt **7b** was treated with a range of acetophenones. Para-substituted acetophenones containing nitro (**2f**), amino (**2e**), chloro (**2b**), or hydroxy (**2d**) groups underwent reaction with equimolar bromide salt **7b** in the presence of 1 equivalent of KOH to afford **3f, 3e, 3b,** and **2d**, respectively, in 80-85% yields (Scheme 9). The reaction is chemoselective, and the crystalline tetrahydroisoquinolines formed were isolated by simple filtration as pure materials. Ortho-substituted compounds such as 2-methyl-acetophenone **2h** and 2-amino-acetophenone **2i**, and meta-substituted 3-nitro- and 3-methoxy acetophenones (**2j** and **2k**) afforded **3h-3k** respectively, in 80-90% yields as coupling products after 45-120 min under similar conditions. All the products were isolated by simple filtration with high yield with a minimum of 2-3 time reproducibility suitable for large-scale reaction.

In parallel, *di-* and *tri*-substituted acetophenones were also screened to examine the influence of electronic and steric effects (Scheme 9). Di-substituted acetophenones such as 2-bromo-6-hydroxy-, 2-hydroxy-4-fluoro-, and 2,3-dichloro-acetophenones (**8a-8c**) afforded efficiently **9a-9c** (80-86%), respectively. Similarly, tri-substituted acetophenones such as 2-hydroxy-3-methyl-4-nitro acetophenone **2r** and highly rich 2,4,6-trimethoxyacetophenone **2t** reacted smoothly to provide the solid products **3r** (85%) and **3t** (88%), respectively. Furthermore, 2-acetylnaphthalene **2ae** and substituted benzofuran acetophenone **2ai** led to **3ae** and **3ai** in 90% and 75% yields, after 30-120 min. The reaction is not limited to aromatic substrates since 1,3-cyclohexanedione **2al** gave the corresponding tetrahydroisoquinoline **3al** in 82% yield.

With this insight, a range of acetyl substituted hetero- aromatic compounds were screened possessing furan, thiophene, or pyridine rings. Thus, 2-acetylfuran **2ab**, 2-acetylthiophene **2aa** and 3-acetylpyridine **2ac** were successfully reacted with bromide salt **7b** to give the coupling compounds **3ab, 3aa**, and **3ac** as pure solids in >80% yields. In addition, very interestingly, benzofuran-2(3H)-one **2ao** led to the noscapine-like product **3ao** in 90% yield with *dr*= 85:15 (Scheme 9).

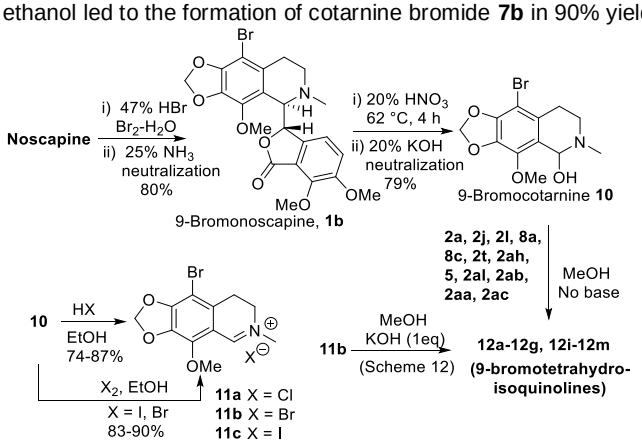
Among the noscapine derivatives synthesized yet, 9-Bromonoscapine **1b** has shown significant higher activity than noscapine identified for its novel tubulin**-**binding anticancer property, while retaining its non-toxic profiles.[20] Importantly, this analogue displays synergism with docetaxel for prostate cancer as seen by cell viability and proliferation assays.[21] Hence, given the potential usefulness of 9-bromonoscapine in the clinic, the synthesis of 9-bromocotarnine halides would be of high interest to access novel drug-inspired compounds.



Scheme 10. Attempts to Synthesize 9-Bromocotarnine.

At the first attempt we tried to brominate at 9- position of cotarnine **1** (Scheme 10). Treatment of cotarnine **1** with *N*-bromo-succinimide in CH_3CN only resulted in oxidation of the benzylic alcohol furnishing **1c** in 83% yield whereas molecular bromination with Br_2 (1 equiv.) and KOAc (1 equiv.) in $CHCl_3$

gave rise to bromination at the 9-position with concomitant oxidation of the benzylic alcohol to form **1d** in 79% yield (Scheme 10). Surprisingly, alternative bromination with Br_2 in ethanol led to the formation of cotarnine bromide **7b** in 90% yield.

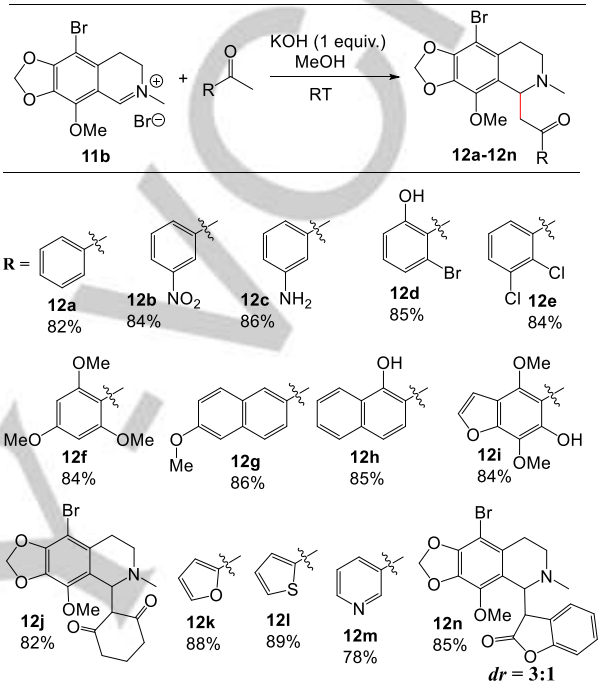


Scheme 11. Synthesis and Condensation of 9-Bromocotarnine 10 with Acetophenones.

Another approach was to convert noscapine into 9-bromonoscapine **1b** by bromination with 47% HBr in Br_2-H_2O, followed by subsequent neutralization with NH_3, in 80% yield.[14b] The latter was oxidized to 9-bromocotarnine **10** in 79% yield (63% from noscapine, 2-steps) with 20% HNO_3 followed by neutralization with 20% KOH (Scheme 11). Following the optimized one-pot procedure for synthesis of tetrahydroiso quinolines from cotarnine **1**, (vide Scheme 3 and 4), 9-bromocotarnine **10** was subjected to condensation with a range of substituted acetophenones (**2a, 2j, 2l, 8a, 8c, 2t, 2ah, 5, 2al, 2ab, 2aa, 2ac**) affording the desired adducts (**12a-12g, 12i-12m**) respectively in good yields (78-91%) (Scheme 11).

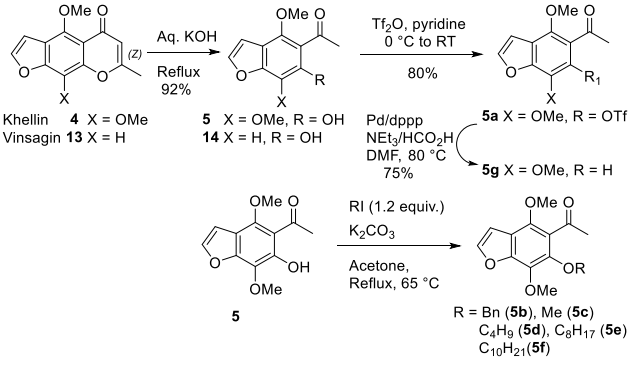
The similar two-step procedure (vide Scheme 8 and 9) for access to 9-bromotetrahydroisoquinolines (Schemes 11 and 12) from 9-bromocotarnine **10** was further examined. In this event, treatment of **10** with hydrohalic acids (HCl, HBr, HI) in ethanol gave the corresponding 9-bromocotarnine salts **11a-11c** in 74-87% yields (Scheme 11). Alternatively, treatment of **10** with molecular halogens (Br_2, I_2) in ethanol also afforded **11b** and **11c**, respectively, in 83-90% yields.

In the context of the exploration of the chemistry of isoquinolin iminium salts, we turned our attention to the coupling reaction from 9-bromo cotarnine salts **11a-11c**. Under similar green conditions, acetophenone **2a** reacted with 9-bromocotarnine bromide salt **11b** in 82% yield after 40 min. The precipitate product 1**2a** was collected by simple filtration. Similarly, mono-substituted acetophenones such as 3-nitroacetophenone **2j** and 3-aminoacetophenone **2l** provided corresponding products **12b** and **12c** in 84 and 86% yields, respectively (Scheme 12). Similarly, di-substituted-acetophenones exemplified by 2-bromo-6-hydroxyacetophenone **8a** and 2,3-dichloro acetophenone **8c**, and tri-substituted 2,4,6-trimethoxy acetophenone **2t**, underwent coupling reaction with **11b** successfully and yielded to **12d-12f**, respectively in >83% yields (Scheme 12). The results with regard to naphthyl derivatives (**2ah** and **2af**), multi-substituted benzofurans (e.g., **5**), 1,3-diketones (e.g. **2al**), and heterocycles (**2ab, 2aa, 2ac, 2ao**) confirm the scope of the reaction. These products (**12g-12n**, respectively) were obtained in good yields (78-89%), as solids after simple filtration after 1-2 h. The latter compound **12n** was formed in 3:1 inseparable mixture of diastereomeric ratio (Scheme 12).

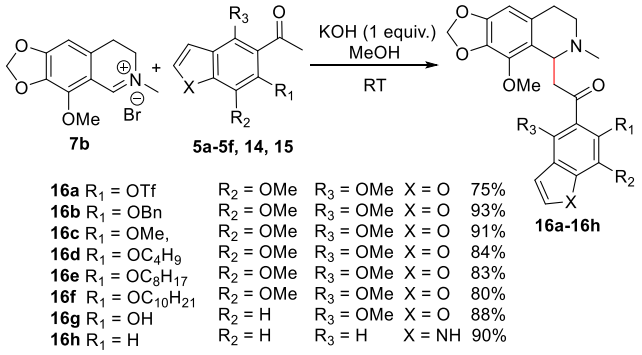


Scheme 12. Synthesis of Functionalized Tetrahydroisoquinolines from 9-Bromocotarnine Bromide Salt 11b

Finally, a series of polysubstituted benzofuran-containing tetrahydroisoquinolines **16a-16h** (Scheme 14) were synthesized from cotarnine bromide **7b** exploiting structural change on khelinone **5** and vinsaginone **14** (Scheme 13).



Scheme 13. Synthesis of 5-Acetyl Benzofurans 5a-5g.



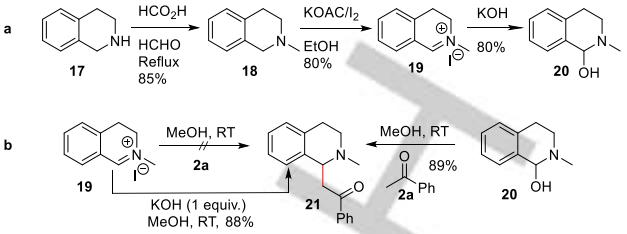
16a R_1 = OTf	R_2 = OMe	R_3 = OMe	X = O	75%
16b R_1 = OBn	R_2 = OMe	R_3 = OMe	X = O	93%
16c R_1 = OMe,	R_2 = OMe	R_3 = OMe	X = O	91%
16d R_1 = OC_4H_9	R_2 = OMe	R_3 = OMe	X = O	84%
16e R_1 = OC_8H_{17}	R_2 = OMe	R_3 = OMe	X = O	83%
16f R_1 = $OC_{10}H_{21}$	R_2 = OMe	R_3 = OMe	X = O	80%
16g R_1 = OH	R_2 = H	R_3 = OMe	X = O	88%
16h R_1 = H	R_2 = H	R_3 = H	X = NH	90%

Scheme 14. Reaction of 5-Acetyl Benzofuran Derivatives and 5-Acetyl Indole with cotarnine bromide 7b.

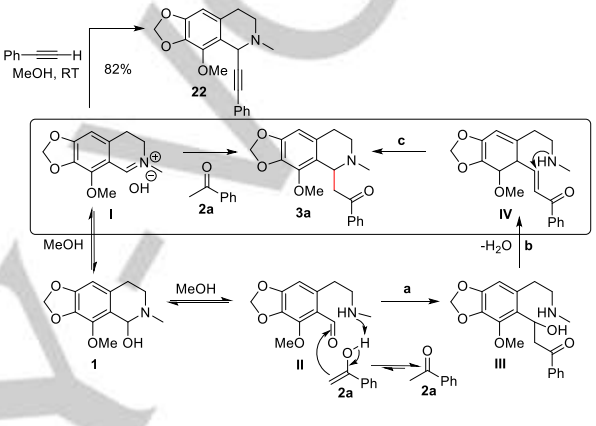
In this event, the coupling partners **5** khelinone and vinsaginone **14** were prepared in >90% yield by treatment of commercially available khellin **4** and visnagin **13**, respectively, with aqueous KOH under reflux condition[16] (Scheme 13). Subsequent triflation of **5** followed by palladium-catalyzed reduction (Pd/dppp) of its triflate derivative **5a** led to **5g** (2 steps, 60% yield).[23] The O-alkylation of **5** under classical basic conditions (K_2CO_3, acetone, reflux, overnight) proceeded smoothly affording polysubstituted benzofuran-containing acetophenones **5b-5f**. The desired coupling took place successfully (75-93%) with these acetophenone partners under basic condition at room temperature (Scheme 14). All compounds were isolated as liquids by a quick and easy chromatography. In addition, 5-acetyl indole **15** under similar conditions afforded corresponding product **16h** in 90% yield.

MECHANISM:

In order to gain some insight into the scope with the counterpart tetrahydroisoquinoline for supporting the mechanism, 2-methyl-1,2,3,4-tetrahydroisoquinolin-1-ol **20** was synthesized in 80% by basic hydrolysis of its salt 2-methyl-3,4-dihydroisoquinolin-2-ium iodide **19 (**Scheme 15a). The latter could be obtained in two steps by *N*-methylation of 1,2,3,4-tetrahydroisoquinoline **17** with 37% formaldehyde and formic acid under reflux condition to yield 2-methyl-1,2,3,4-tetrahydro isoquinoline **18** (85% yield) which was subjected to reaction with I_2/KOAc in ethanol. Thus, reaction of 2-methyl-1,2,3,4-tetrahydroisoquinolin-1-ol **20** with acetophenone **2a** occurred leading to the coupling product **21** in 89% yield, indicating that the presence of electron-donating groups on the aromatic ring of the cotarnine derivative is not crucial for the reaction to proceed (Scheme 15 b). Additionally, the reaction with the iminium form **19** of **20** was successful only in the presence of KOH to give **21** in 88% yield**.**



Scheme 15. (a) Synthesis of 2-Methyl-3,4-dihydroisoquinoline 20. (b) Reaction of 20 and its salt 19 with acetophenone 2a.



Scheme 16. Proposed Mechanism[27]

In the case of the one-step procedure, the most plausible mechanism for the coupling reaction from cotarnine **1** would involve the formation of cotarnine iminium hydroxide intermediate **I** in situ in MeOH **(**not detectable by ^{1}H NMR spectroscopy in CD_3OD) (Scheme 16). This would release hydroxide that could deprotonate acetophenone **2a** and allow a Mannich-type reaction[23] (**3a**) to occur. It is supported by the incorporation of phenylacetylene into cotarnine under base-free conditions at room temperature to afford 1-phenylacetylene-1,2,3,4-tetrahydroisoquinolines **22** in 82% yield.

Consequently, and given the low acidity of phenylacetylene, the alternative mechanism proposed by Kanai and co-workers[24] in the case of cyclic hemiaminals, does not seem a likely explanation (Scheme 16). More precisely, cotarnine as a cyclic hemiaminal would exist in equilibrium with linear amino-aldehyde **II**. This mechanism is a multi-step process: (a) deprotonation of the enol form of acetophenone **2a** by the secondary amine moiety of **II** through H-bonding, thus activating it for nucleophilic addition, affording aldol **III**; (b) dehydration or crotonization to lead to enone **IV**; and (c) an intramolecular aza-Michael reaction to produce **3a**.

CONCLUSIONS

We have described a practical and efficient one-step synthesis of 1-substituted-1,2,3,4-tetrahydroisoquinolines in excellent yields from cotarnine and various aromatic and heteroaromatic

acyl/aryl ketonees bearing at least one α-hydrogens. The present work provides an attractive strategy for construction of structurally diverse noscapinoids. The products were isolated by simple filtration without further chromatography. Other features of this reaction include environmentally benign solvent/base-free protocol, short periods of 0.5-1 h, scalability to multi-gram quantities and excellent chemoselectivity and moderate diastereoselectivities. The complementary two-step procedure through cotarnine halide salts appears to be less efficient in terms of yields. Targeted biological activities of these isoquinoline-derived alkaloids will be reported in due course.

Experimental Section

General information. All reactions were performed under general atmosphere unless otherwise noted. Methanol, ethanol was purchased from Sigma Aldrich (99.9%). (*S,R*)-Noscapine was purchased from Sigma-Aldrich France with 97% purity. All acetophenones were obtained from Sigma, Fluka, TCI, Alfa-Aesar, VWR, or Across Organics. Reactions were followed with TLC (0.25 mm silica gel 60-F plates). Visualisation was accomplished by UV light and Dragendorff stain. Flash chromatography was carried out on silica gel 320-400 mesh. Yields refer to chromatographically and spectroscopically pure materials. ^{1}H NMR spectra were recorded at 300 MHz.^{13}C NMR spectra were recorded at 75 MHz with complete proton decoupling. Chemical shifts are reported in ppm relative to the residual solvent peak ($CDCl_3$/CD_2Cl_2, CD_3CN/CD_3SOCD_3) as the internal reference, coupling constants are given in Hertz. Peak assignment was unambiguously performed using HMQC and HMBC technique. NOESY studies on the selected compound were performed on 400MHz NMR spectrometer. Melting points were determined by capillary method and are uncorrected. HRMS Spectra were obtained from Fédération de Recherche Physique et Chimie du Vivant (FR2708: CBM/ICOA), Plate-Forme de Spectrométrie de Masse Haute Résolution, Institut de Chimie Organique et Analytique, UMR 7311, Université d'Orléans.

4-methoxy-6-methyl-5,6,7,8-tetrahydro-[1,3]dioxolo[4,5-g]isoquinolin-5-ol (1). An oven-dried, 250 mL round bottom flask equipped with a magnetic stir bar was charged with (*S,R*)-Noscapine (20 g**,** 24.2 mmol). 14% HNO_3 (150 mL) was added carefully and dropwise for 5 min with slow stirring at room temperature. The resulting mixture was transferred to an oil bath and heated to 57 °C for 2 h. After 2 h, once no more precipitate was formed, the reaction was removed from oil bath and cooled at room temperature for 0.5 h. The mixture was then filtered in a sintered funnel with negative pressure of water to afford opianic acid (solid). The yellow filtrate was neutralized slowly with 25% KOH with continuous shaking until yellow precipitate was formed (pH=11). The precipitate was filtered, washed with cold distilled water (5 mL), and dried to give cotarnine **1** (10.4 g, 90%) as a yellowish crystalline solid. Mp: 135 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.32 (s, 1H), 5.88 (s, 2H), 5.43 (d, *J* = 3.9 Hz, 1H), 4.04 (s, 3H), 3.08–3.03 (m, 1H), 2.89–2.85 (m, 1H), 2.64–2.63 (m, 1H), 2.6 (s, 3H), 2.24 (d, *J* = 3.9 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): *δ* 148.9, 140.4, 134.1, 128.9, 122.3, 102.5, 100.7, 79.0, 59.7, 43.4, 40.9, 28.8; HRMS (ESI) *m/z* $[M\text{-}OH]^+$ calcd for $C_{12}H_{14}NO_3$ 220.0968, found 220.0966.

(*S*)-3-((*R*)-9-bromo-4-methoxy-6-methyl-5,6,7,8-tetrahydro-[1,3]dioxolo[4,5-g]isoquinolin-5-yl)-6,7-dimethoxyisobenzofuran-1(3H)-one (**1b)**. To a flask containing noscapine (4 g, 12.1 mmol); 4 ml of 47% HBr solution is added and stirred for 5 minute. To the reaction mixture freshly prepared bromine water (3% Br_2, Br_2-H_2O, 30-40 ml) was added drop wise until an orange precipitate appeared. The reaction mixture was then stirred at room temperature for 30 minute. The above mixture was neutralized by 25% NH_3 and was added till *pH*=11 to afford white precipitate. The solid precipitate was filtered, dried and recrystallized with ethanol to afford 9-bromo noscapine in **1b** 80% yield (3.81 g).Grey solid. Mp: 169 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.02 (d, *J* = 8.1 Hz, 1H), 6.30 (d, 1H, *J* = 8.1 Hz), 6.10 (m, 2H), 5.49 (d, *J* = 3.9 Hz, 1H), 4.33–4.32 (m, 1H), 3.97 (s, 3H), 4.08 (s, 3H), 3.87 (s, 3H), 2.72–2.59 (m, 2H), 2.50 (s, 3H), 2.47–2.21 (m, 1H), 1.97–1.91 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): *δ* 168.0, 152.3, 147.8, 146.6, 141.2, 139.9, 134.2, 130.3, 119.6, 118.3, 117.5, 102.3, 101.1, 95.6, 81.2, 62.3, 60.9, 59.4, 56.8, 48.4, 45.1, 25.9; MS (ESI) *m/z* $[M+H]^+$ calcd for $C_{22}H_{23}BrNO_7$ 492.07, found 492.15.

9-bromo-4-methoxy-6-methyl-5,6,7,8-tetrahydro-[1,3]dioxolo[4,5-g]isoquinolin-5-ol (10). An oven-dried, 100 mL round bottom flask equipped with a magnetic stir bar was charged with 9-bromo-(*S,R*)-Noscapine **1b** (3.5 g**,** 7.12 mmol). 20% HNO_3 (15mL) was added carefully and drop wise for 5 min with slow stirring at room temperature. The resulting mixture was transferred to an oil bath and heated to 62°C for 2 h. After 2 h, the reaction mixture was cooled at room temperature. The mixture was then extracted with 25 ml of dichloromethane. The water layer was then neutralized with 25% KOH with continuous shaking until yellowish precipitate was formed (pH=11). The precipitate was filtered, washed with cold distilled water (5 mL), and dried to give 9-bromo-cotarnine **10** as a yellowish solid product (1.77 g, 79%). Mp: 142 °C; ^{1}H NMR (300 MHz, $CDCl_3$): *δ* 5.98 (d, *J* = 2.7 Hz, 2H), 4.33–4.32 (m, 1H), 5.41 (s, 1H), 4.03 (s, 3H), 3.11–3.02 (m, 1H), 2.73–2.67 (m, 3H), 2.59 (s, 3H), 2.28 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): *δ* 147.0, 139.8, 134.4, 128.2, 124.0, 101.2, 95.9, 78.7, 59.8, 43.1, 40.7, 28.8; HRMS (ESI) *m/z* $[M\text{-}OH]^+$ calcd for $C_{12}H_{13}BrNO_3$ 298.0073, 300.0054 found 298.0071, 300.0051.

General procedure GP-1 (preparation of cotarnine halide salts 7a-7c from 1 and 11a-11c from 10)
An oven-dried, 10 mL round bottom flask equipped with a magnetic stir bar was charged with cotarnine **1** (1g, 4.21 mmol) or 9-bromo cotarnine **10** (1g, 3.17 mmol) and subsequently diluted with absolute ethanol (2 mL). The resulting solution was stirred under ice cooling for 5 min. The turbidity was observed in the reaction medium caused by the solubility of cotarnine. To this solution was added drop wise 25% HCl or 47% HBr or 48% HI in ethanol until it was acidic (pH=4-5) and the mixture became clear greenish-yellow. Slow addition of dry acetone (2 mL) led generally to the formation of a white insoluble precipitate. If not, the above mixture was allowed to store at -15 °C for 2-3 h. Whitish yellow crystals of cotarnine halide **7a, 7b, 7c and 11a, 11b, 11c** were collected by filtration, *washed* by rinsing with cold acetone, and dried under vacuum.

General procedure GP-2 (preparation of cotarnine halide salts 7b-7c from 1 and 11b-11c from 10):
To cotarnine **1** (1g, 4.21 mmol) or 9-bromo cotarnine **10** (1g, 3.17 mmol) in 2 ml ethanol under room temperature, bromine (Br_2, 4.21 mmol)) or Iodine (I_2, 4.21 mmol) in 0.5 ml ethanol were added. The precipitate formed during addition were filtered after 30 minute, washed by rinsing cold acetone and dried under vacuum to afford Yellow crystals of cotarnine halide **7b, 7c and 11b, 11c.**

General procedure GP-3A (Synthesis of 1,2,3,4-tetrahydroisoquinoline from 1 and 10):
In 10 mL round bottom flask, 2 mmol of cotarnine **1** or 9-bromocotarnine **10** was dissolved in 1 ml of methanol. The solution is stirred for 2 minute (gently warmed to dissolve **10** where ever necessary). To this solution, 2 mmol of aryl/alkyl ketones/lactones were added and stirred for 30-120 minutes (in most of the cases, the spontaneous condensation product precipitated during 10 minutes of stirring). The product was collected by simple filtration with Whatman filter paper-40, washed with cold methanol (2 mL), and dried under vacuum. Sometime the liquid product was subjected to very short column purification.

General procedure GP-3B (Synthesis of 1,2,3,4-tetrahydroisoquinoline from cotarnine salts 7b and 11b):
In 10 mL round bottom flask, 2 mmol of cotarnine salt **7b** or 9-bromocotarnine salt **11b** was dissolved in 1 ml of methanol and 2 equivalent of potassium hydroxide (KOH, Finely powdered) was added. The solution is stirred for 2 minute. To this solution, 2 mmol of aryl/alkyl ketones/lactones were added and stirred for 30-120 minutes. The product precipitate was formed during stirring. The product was collected by simple filtration with Whatman filter paper-40, washed with cold methanol (2 mL), and dried under vacuum. Sometime the liquid product was subjected to very short column purification.

4-methoxy-6-methyl-7,8-dihydro-[1,3]dioxolo[4,5-g]isoquinolin-6-ium chloride (7a). Following general procedure GP-1, **7a** (970 mg, 90%) was obtained from cotarnine **1** as white solid. Mp: 197 °C; R_f = 0.5 (1:1 H_2O:MeOH); ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.16 (s, 1H), 6.47 (s, 1H), 6.06 (s, 2H), 4.17 (s, 3H), 4.10 (d, J = 8.1 Hz, 2H), 4.04 (s, 3H), 3.23 (t, J = 7.8 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 168.2, 158.2, 145.0, 135.0, 134.3, 110.86, 103.3, 102.7, 60.5, 49.5, 48.2, 26.2; HRMS (ESI) m/z [M-OH]$^+$ calcd for $C_{12}H_{14}NO_3$ 220.0968, found 220.0966.

4-methoxy-6-methyl-7,8-dihydro-[1,3]dioxolo[4,5-g]isoquinolin-6-ium bromide (7b). Following general procedure GP-1, **7b** (949 mg, 75%) was obtained from cotarnine **1** as yellow solid [alternatively, following general procedure GP-2, **7b** (1.13 g, 90%) was obtained from **1** treating with Br_2]. Mp: 201 °C; R_f = 0.5 (1:1 H_2O:MeOH); ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.08 (s, 1H), 6.47 (s, 1H),6.06 (s, 2H), 4.17 (s, 3H), 4.07 (d, 2H, J = 8.1 Hz), 3.98 (s, 3H), 3.21 (t, 2H, J = 8.1 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ 160.1, 158.3, 144.9, 134.9, 134.4, 110.9, 103.4, 102.7, 60.6, 49.6, 48.4, 26.3; HRMS (ESI) m/z [M-OH]$^+$ calcd for $C_{12}H_{14}NO_3$ 220.0968, found 220.0966.

4-methoxy-6-methyl-7,8-dihydro-[1,3]dioxolo[4,5-g]isoquinolin-6-ium iodide (7c). Following general procedure GP-1, **7c** (1.28 g, 88%) was obtained from cotarnine **1** as brown solid [alternatively, following general procedure GP-2, **7c** (1.34 g, 92%) was obtained from **1** treating with I_2]. Mp: 180 °C; R_f= 0.5 (1:1 H_2O:MeOH); ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.01(s, 1H), 6.49 (s, 1H), 6.09 (s, 2H), 4.21 (s, 3H), 4.01 (d, J = 8.4 Hz, 2H), 3.91 (s, 3H), 3.27 (t, J = 8.1 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 160.1, 158.4, 144.9, 134.4, 110.9, 103.5, 102.8, 60.7, 50.0, 49.0, 26.3; HRMS (ESI) m/z [M-OH]$^+$ calcd for $C_{12}H_{14}NO_3$ 220.0968, found 220.0966.

9-bromo-4-methoxy-6-methyl-7,8-dihydro-[1,3]dioxolo[4,5-g]isoquinolin-6-ium chloride (11a). Following general procedure GP-1, **11a** (782mg, 74%) was obtained from 9-bromo cotarnine **10** as white solid. Mp: 115 °C; R_f = 0.5 (1:1 H_2O:MeOH); ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.23 (s, 1H), 6.17 (s, 2H), 4.21 (s, 3H), 4.09 (d, J = 8.1 Hz, 2H), 4.02 (s, 3H), 3.30 (t, 2H, J = 7.8 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ160.9, 156.1, 144.9, 135.1, 133.9, 112.6, 103.5, 96.6, 61.4, 49.8, 48.7, 26.1; HRMS (ESI) m/z [M-OH]$^+$ calcd for $C_{12}H_{13}BrNO_3$ 298.0073, 300.0054 found 298.0071, 300.0053.

9-bromo-4-methoxy-6-methyl-7,8-dihydro-[1,3]dioxolo[4,5-g]isoquinolin-6-ium bromide (11b). Following general procedure GP-1, **11b** (1.109 g, 85%) was obtained from 9-bromo cotarnine **10** as yellow solid [alternatively, following general procedure GP-2, **11b** (995 mg, 83%) was obtained from **10** treating with Br_2]. Mp: 97 °C; R_f = 0.5 (1:1 H_2O:MeOH); ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.16 (s, 1H), 6.18 (s, 2H), 4.23 (s, 3H), 4.03 (d, J = 8.1 Hz, 2H), 3.98 (s, 3H), 3.32 (t, J = 7.8 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 160.3, 155.8, 144.4, 134.7, 133.4, 109.6, 103.1, 96.3, 61.0, 49.7, 49.5, 48.6, 25.8; HRMS (ESI) m/z [M-OH]$^+$ calcd for $C_{12}H_{13}BrNO_3$ 298.0073, 300.0054 found 298.0069, 300.0052.

9-bromo-4-methoxy-6-methyl-7,8-dihydro-[1,3]dioxolo[4,5-g]isoquinolin-6-ium iodide (11c). Following general procedure GP-1, **11c** (1.172 g, 87%) was obtained from cotarnine **10** as brown solid [alternatively, following general procedure GP-2, **11c** (1.21 g, 90%) was obtained from **10** treating with I_2]. Mp: 180 °C; R_f = 0.5 (1:1 H_2O:MeOH); ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.14 (s, 2H), 6.17 (s, 2H), 4.22 (s, 3H), 4.02 (t, J = 3.6 Hz, 2H), 3.92(s, 3H), 3.29 (t, J = 8.1 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 160.0, 155.9, 144.4, 134.8, 133.2, 112.3, 109.6, 103.1, 96.4, 60.9, 50.0, 49.0, 25.6; HRMS (ESI) m/z [M-OH]$^+$ calcd for $C_{12}H_{13}BrNO_3$ 298.0073, 300.0054 found 298.0070, 300.0052.

4-methoxy-6-methyl-7,8-dihydro-[1,3]dioxolo[4,5-g]isoquinolin-5(6H)-one (1c). In an oven-dried 25 mL round bottom flask equipped with a magnetic stir bar was charged with 2 mmol of cortarnine **1** (0. 476 g**,** 2 mmol) in 5 ml of chloroform. To this 2 mmol (0.352 g) of *N*-bromosuccinimide is added. The mixture was stirred for overnight. The resulting mixture was then extracted with 10 ml of water. The organic layer was concentrated and subjected to column. The pure product was isolated as crispy liquid **1c** in 83% yield (0.391 g). ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.36 (s, 1H), 5.96 (s, 2H), 4.03 (s, 3H), 3.42 (t, J = 6.3 Hz, 2H),3.11 (s, 3H), 2.81 (t, 2H, J = 6.3 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ 147.0, 139.8, 134.7, 128.2, 124.0, 109.6, 101.2, 96.0, 78.7, 59.8, 43.1, 40.7, 28.8; MS (ESI) m/z [M+H]$^+$ calcd for $C_{12}H_{14}NO_4$ 236.09, found 236.08.

9-bromo-4-methoxy-6-methyl-7,8-dihydro-[1,3]dioxolo[4,5-g]isoquinolin-5(6H)-one (1d). In an oven-dried 25 mL round bottom flask equipped with a magnetic stir bar was charged with 2 mmol of cortarnine **1** (0. 476 g**,** 2 mmol) in 5 ml of chloroform. To this 2 mmol (0.192 g) of KOAc added. The mixture was stirred for overnight. The resulting mixture was then extracted with 5 ml of sodium thiosulfate and 10 ml brine water. The organic layer was concentrated and subjected to column chromatography. The pure product was isolated as liquid **1d** in 79% yield (0.498 g). ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.06 (s, 2H), 4.03 (s, 3H), 3.45 (t, J = 6.3 Hz, 2H), 3.12 (s, 3H), 2.92 (t, J = 6.9 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 147.0, 139.8, 134.7, 128.2, 124.0, 109.6, 101.2, 96.0, 78.7, 59.8, 43.1, 40.7, 28.8; MS (ESI) m/z [M+H]$^+$ calcd for $C_{12}H_{13}BrNO_4$ 314.00, found 314.01.

1-(6-hydroxy-4,7-dimethoxybenzofuran-5-yl)ethan-1-one (5). An oven-dried, 500 mL round bottom flask equipped with a magnetic stir bar was charged with Khellin **4** (10 g**,** 38.5 mmol) and subsequently diluted with distilled water (250 mL), and the resulting mixture was stirred at room temperature for 10 min. A solution of KOH (7.54 g, 3.5 equiv., 134.6 mmol) in distilled water (20 mL) was then added slowly for 5-10 min. After completion, the reaction was further stirred for 20 minute at room temperature. Next, the mixture was refluxed at 105 ^{o}C for 3-4 h. The reaction mixture was cooled down and neutralized with 3M HCl through drop by drop addition. The orange yellow precipitate was collected by filtration, *washed* by rinsing with cold water, and dried under vacuum to afford 1-(6-hydroxy-4,7-dimethoxybenzofuran-5-yl) ethanone **5** in 95% yield (8.623g**).** Yellowish solid: Mp: 99 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.52 (s, 1H), 6.87 (s, 1H), 4.13 (s, 3H), 4.12 (s, 3H), 2.74 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 205.2, 153.5, 152.3, 151.6, 143.8, 128.8, 110.8, 110.6, 105.7, 61.0, 60.5, 32.2; MS (ESI) m/z [M+H]$^+$ calcd for $C_{12}H_{13}O_5$ 237.23, found 237.55.

5-acetyl-4,7-dimethoxybenzofuran-6-yl trifluoromethanesulfonate (5a). To a solution of 1-(6-hydroxy-4,7-dimethoxybenzofuran-5-yl) ethanone **5** (2.36 g, 10 mmol) in pyridine (10 mL) at ice-cold temperature was added triflic anhydride (12 mmol, 3.39 mL) drop by drop. The reaction was stirred at room temperature for 12 h. After removing the solvent, the residue was dissolved in ethyl acetate and hexane mixture (1:1). Following flash chromatography, triflate **5a** was isolated as gummy orange liquid (2.944 g, 80%); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.71 (d, J = 3 Hz, 1H), 6.97 (d, J = 3 Hz, 1H), 4.19 (s, 3H), 4.03 (s, 3H), 2.59 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 198.8, 147.4, 146.8, 145.4, 134.5, 133.5, 123.0, 121.1, 121.7, 116.8, 105.8, 61.9, 61.9, 61.5, 32.6; MS (ESI) m/z [M+H]$^+$ calcd for $C_{13}H_{12}F_3O_7S$ 369.03, found 369.05.

1-(4,7-dimethoxybenzofuran-5-yl)ethan-1-one (5g). To a solution of **5a** (736 mg, 2 mmol), $Pd(PPh_3)_2Cl_2$ (28 mg, 0.02 equiv.) and DPPP (33 mg, 0.04 equiv.) in DMF (5 mL) was successively added EtN_3 (606 mg, 3 equiv.) and HCO_2H (184 mg, 2 equiv.). The resulting solution was heated at 60 °C for 2 h. After cooling, the reaction mixture was extracted with diethyl ether, washed with brine, and dried. The combined organic layers were concentrated and subjected to flash chromatography to afford **5g** (330 mg, 75%) as white solid. Mp: 110 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.64 (d, J = 2.1 Hz, 1H), 7.25 (s, 1H), 6.96 (d, J = 2.4 Hz, 1H), 4.06 (s, 3H), 4.0 (s, 3H), 2.69 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 198.7, 148.9, 148.2, 145.1, 141.6, 124.8, 121.2, 106.7, 105.9, 61.2, 56.3, 31.6; MS (ESI) *m/z* $[M+H]^+$ calcd for $C_{12}H_{13}O_4$ 221.08, found 221.18.

General procedure GP-4 (preparation of O-alkylated acetophenones 5b-5f from 5). To a solution of phenol **5** (2 mmol) in 10 mL acetone, alkyl halide (BnBr/MeI/n-C_4H_9I/ $C_8H_{17}I$/$C_{10}H_{21}I$, 2.5 equiv) and K_2CO_3 (5.0 equiv) was added. The flask is transferred to a reflux bath maintained at 65 °C. The mixture is cooled after overnight reflux. The insoluble K_2CO_3 is filtered off. The filtrate is concentrated and subjected to column chromatography to afford analytically pure compound **5b-5f** as oil in good yields.

1-(6-(benzyloxy)-4,7-dimethoxybenzofuran-5-yl)ethan-1-one (5b). Following general procedure GP-4, **5b** (593 mg, 91%) was obtained as orange liquid. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.6 (d, J = 2.4 Hz, 1H), 7.45–7.32 (m, 5H), 6.88 (d, J = 2.4 Hz, 1H), 5.08 (s, 2H), 4.09 (s, 3H), 3.99 (s, 3H), 2.43 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 202.1, 148.7, 144.7, 144.1, 144.1, 137.1, 134.2, 128.6, 128.5, 128.2, 124.6, 116.6, 105.1, 76.7, 61.2, 32.8; MS (ESI) *m/z* $[M+H]^+$ calcd for $C_{19}H_{19}O_5$ 327.12, found 327.30.

1-(4,6,7-trimethoxybenzofuran-5-yl)ethan-1-one (5c). Following general procedure GP-4, **5c** (465 mg, 93%) was obtained as orange liquid. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.57 (d, J =2.4 Hz, 1H), 6.86 (d, J =2.4 Hz, 1H), 4.08 (s, 3H), 3.98 (s, 3H), 3.90 (s, 3H), 2.52 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 202.0, 148.6, 145.5, 144.6, 144.0, 134.3, 124.7, 116.5, 105.0, 62.4, 61.3, 61.1, 32.8; MS (ESI) *m/z* $[M+H]^+$ calcd for $C_{13}H_{15}O_5$ 251.09, found 251.17.

1-(6-butoxy-4,7-dimethoxybenzofuran-5-yl)ethan-1-one (5d). Following general procedure GP-4, **5d** (531 mg, 91%) was obtained as orange liquid.^{1}H NMR (300 MHz, $CDCl_3$): δ 7.56 (d, J = 2.4 Hz, 1H), 6.86 (d, J = 2.4 Hz, 1H), 3.97 (s, 3H), 4.05 (s, 3H), 2.52 (s, 3H), 1.74–1.64 (m, 2H), 1.47–1.40 (m, 2H), 0.96 (t, J = 7.2 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 202.2, 148.7, 144.9, 144.5, 143.9, 134.4, 124.6, 116.3, 105.0, 75.0, 61.3, 61.1, 32.9, 32.2, 19.1, 13.9; MS (ESI) *m/z* $[M+H]^+$ calcd for $C_{16}H_{21}O_5$ 293.14, found 293.24.

1-(4,7-dimethoxy-6-(octyloxy)benzofuran-5-yl)ethan-1-one (5e). Following general procedure GP-4, **5e** (619 mg, 89%) was obtained as orange liquid. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.57 (d, J = 2.1 Hz, 1H), 6.86 (d, J = 2.1 Hz, 1H), 4.06 (s, 3H), 4.04–4.00 (m, 2H), 3.98 (s, 3H), 2.52 (s, 3H), 1.73–1.68 (m, 2H), 1.39–1.28 (m, 12H), 0.88 (t, J = 5.4 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 202.1, 148.7, 144.9, 144.5, 144.0, 124.6, 116.3, 105.0, 75.3, 61.3, 61.1, 32.9, 31.9, 30.1, 29.4, 29.3, 25.9, 22.7, 14.1; MS (ESI) *m/z* $[M+H]^+$ calcd for $C_{20}H_{29}O_5$ 349.20, found 349.25.

1-(6-(decyloxy)-4,7-dimethoxybenzofuran-5-yl)ethan-1-one (5f). Following general procedure GP-4, **5f** (661 mg, 88%) was obtained as orange liquid. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.56 (d, J = 2.1 Hz, 1H), 6.86 (d, J = 2.1 Hz, 1H), 4.05 (s, 3H), 4.02–4.00 (m, 2H), 3.97 (s, 3H), 2.52 (s, 3H), 1.75–1.66 (m, 2H), 1.39–1.26 (m, 14H), 0.87 (t, J = 6.3 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 202.1, 148.7, 144.9, 144.5, 143.9, 134.4, 124.6, 116.3, 105.0, 75.3, 61.3, 61.1, 32.8, 31.9, 30.1, 29.6, 29.4, 29.3, 25.9, 22.7, 14.1; MS (ESI) *m/z* $[M+H]^+$ calcd for $C_{22}H_{33}O_5$ 377.23, found 377.27.

2-(4-methoxy-6-methyl-5,6,7,8-tetrahydro-[1,3]dioxolo[4,5-g]isoquinolin-5-yl)-1-phenylethan-1-one (3a). Following general procedure GP-3A, **3a** (6.18 g, 92%) was obtained from **1** (20 mmol) and **2a** (20 mmol) as white powder [alternatively, following GP-3B, **3a** (85%) was obtained from **7b** and **2a**]. Mp: 130 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.00 (d, J = 6 Hz, 1H), 7.54 (d, J = 7.2 Hz, 1H), 7.45 (t, J = 7.2 Hz, 2H), 5.85 (s, 2H), 6.31 (s, 1H), 4.46 (dd, J = 7.2, 4.5 Hz, 1H), 3.94 (s, 3H), 3.23–3.09 (m, 2H), 2.92–2.73 (m, 2H), 2.40–2.39 (m, 1H), 2.37 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 199.3, 148.1, 140.6, 137.7, 134.2, 133.0, 128.8, 128.6, 128.4, 122.7, 101.0, 100.8, 59.3, 55.5, 44.8, 44.0 ,42.3, 24.1; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{20}H_{22}NO_4$, 340.1549, found 340.1542.

1-(4-chlorophenyl)-2-(4-methoxy-6-methyl-5,6,7,8-tetrahydro-[1,3]dioxolo[4,5-g]isoquinolin-5-yl)ethan-1-one (3b). Following general procedure GP-3A, **3b** (689 mg, 92%) was obtained from **1** and **2b** as white powder [alternatively, following GP-3B, **3b** (80%) was obtained from **7b** and **2b**]. Mp: 127 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.95 (d, J = 8.7 Hz, 2H), 7.39 (d, J = 8.4 Hz, 2H), 5.84 (s, 2H), 6.29 (s, 1H), 4.42 (t, J = 6.0 Hz, 1H), 3.93 (s, 3H), 3.36–3.29 (m 1H), 3.17–3.07 (m, 3H), 2.86–2.71 (m, 2H), 2.43–2.38 (m, 1H), 2.34 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 197.7, 147.8, 140.1, 138.9, 135.6, 133.8, 129.7, 128.7, 128.0, 121.9, 102.6, 100.5, 59.1, 55.2, 44.3, 43.7, 41.8, 23.4; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{20}H_{22}ClNO_4$ 374.1159, found 374.1154.

1-(4-bromophenyl)-2-(4-methoxy-6-methyl-5,6,7,8-tetrahydro-[1,3]dioxolo[4,5-g]isoquinolin-5-yl)ethan-1-one (3c). Following general procedure GP-3A, **3c** (738 mg, 88%) was obtained from **1** and **2c** as white crystalline solid. Mp: 121 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.88 (d, J = 8.4 Hz, 2H), 7.60 (d, J = 9.0 Hz, 2H), 6.30 (s, 1H), 5.85 (s, 2H), 4.41 (dd, J = 6.0, 3.0 Hz, 1H), 3.94 (s, 3H), 3.32–3.02 (m, 3H), 2.86–2.74 (m, 2H), 2.45–2.37 (m, 1H), 2.34 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 197.9, 147.8, 140.1, 136.0, 133.8, 131.7, 129.8, 128.0, 127.7, 121.8, 102.6, 100.5, 59.1, 55.2, 44.3, 43.7, 41.8, 23.5; MS (ESI) *m/z* $[M+H]^+$ calcd for $C_{20}H_{21}BrNO_4$ 418.06, found 418.13.

1-(4-hydroxyphenyl)-2-(4-methoxy-6-methyl-5,6,7,8-tetrahydro-[1,3]dioxolo[4,5-g]isoquinolin-5-yl)ethan-1-one (3d). Following general procedure GP-3A, **3d** (641 mg, 90%) was obtained from **1** and **2d** as white powder [alternatively, following GP-3B, **3d** (81%) was obtained from **7b** and **2d**]. Mp: 141 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.77 (d, J = 8.1 Hz, 2H), 6.72 (d, J = 8.1 Hz, 2H), 6.72 (d, J = 8.1 Hz, 2H), 6.31 (s, 1H), 5.85 (s, 2H), 6.31 (s, 1H), 3.92 (s, 3H), 4.58–4.56 (m, 1H), 3.28–3.15 (m, 2H), 3.07–3.02 (m, 1H), 2.97–2.78 (m, 2H), 2.52–2.45 (m, 1H), 2.42 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 197.2, 163.9, 147.9, 140.2, 133.9, 131.0, 130.8, 127.6, 122.1, 116.2, 116.0, 102.5, 100.5, 59.2, 54.9, 44.3, 42.8, 41.7, 26.1, 23.6; MS (ESI) *m/z* $[M+H]^+$ calcd for $C_{20}H_{22}NO_5$ 356.15, found 356.15.

1-(4-aminophenyl)-2-(4-methoxy-6-methyl-5,6,7,8-tetrahydro-[1,3]dioxolo[4,5-g]isoquinolin-5-yl)ethan-1-one (3e).). Following general procedure GP-3A, **3e** (654 mg, 92%) was obtained from **1** and **2e** as white powder [alternatively, following GP-3B, **3e** (85%) was obtained from **7b** and **2e**]. Mp: 199 °C; ^{1}H NMR (300 MHz, CD_2Cl_2): δ 7.88 (d, J = 8.1 Hz, 1H), 6.57 (d, J = 8.1 Hz, 2H), 6.30 (s, 1H), 5.84 (s, 2H), 4.49–4.45 (m, 1H), 4.05 (s, 2H), 3.93 (s, 3H), 3.22–3.01 (m, 3H), 2.94–2.73 (m, 2H), 2.52–2.42 (m, 1H), 2.38 (s, 3H); ^{13}C NMR (75 MHz, DMSO–D_6): δ 195.3, 153.3, 147.1, 139.7, 133.6, 130.3, 127.7, 124.9, 122.4, 112.4, 102.5, 100.3, 58.9, 54.9, 43.4, 41.9, 40.0, 22.8; MS (ESI) *m/z* $[M]^+$ calcd for $C_{20}H_{22}N_2O_4$ 354.16, found 354.18.

2-(4-methoxy-6-methyl-5,6,7,8-tetrahydro-[1,3]dioxolo[4,5-g]isoquinolin-5-yl)-1-(4-nitrophenyl)ethan-1-one (3f). Following general procedure GP-3A, **3f** (694 mg, 90%) was obtained from **1** and **2f** as light yellow solid [alternatively, following GP-3B, **3f** (81%) was obtained from **7b** and **2f**]. Mp: 158 °C; ^{1}H NMR (300 MHz,

$CDCl_3$): δ 8.32 (d, J = 8.4 Hz, 1H), 8.14 (d, J = 8.4 Hz, 2H), 5.86 (s, 2H), 6.31 (s, 1H), 4.37–4.33 (s, 1H), 3.97 (s, 3H), 3.33–3.08 (m, 3H), 2.92–2.73 (m, 2H), 2.44–2.37 (m, 1H), 2.33 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 197.7, 150.0, 148.0,141.9, 140.0, 133.9, 129.2, 128.0, 123.7, 121.2, 102.7, 100.5, 59.2, 55.3, 44.4, 44.3, 41.8, 23.2; MS (ESI) *m/z* $[M+H]^+$ calcd for $C_{20}H_{23}N_2O_6$ 385.14, found 385.20.

1-(2-hydroxyphenyl)-2-(4-methoxy-6-methyl-5,6,7,8-tetrahydro-[1,3]dioxolo[4,5-g]isoquinolin-5-yl)ethan-1-one (3g). Following general procedure GP-3A, **3g** (634 mg, 89%) was obtained from **1** and **2g** as brown solid. Mp: 88 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.85 (d, J = 8.1 Hz, 2H), 7.47 (t, J = 7.2 Hz, 2H), 7.00 (d, J = 9.4 Hz, 1H), 6.90 (t, J = 8.1 Hz, 1H), 6.32 (s, 1H), 5.86 (d, J = 2.7 Hz, 1H), 4.71–4.43 (dd, J = 8.1, 4.5 Hz, 1H), 3.94 (s, 3H), 3.25–3.14 (m, 2H), 2.93–2.76 (m, 2H), 2.49–2.47 (m, 1H), 2.40 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 205.2, 162.5, 147.9, 140.1, 135.9, 133.7, 130.1, 128.0, 121.6, 119.8, 118.7, 118.4, 102.6, 100.5, 59.1, 55.4, 44.4, 43.3, 41.9, 23.5; MS (ESI) *m/z* $[M+H]^+$ calcd for $C_{20}H_{22}NO_5$ 356.15, found 356.26.

2-(4-methoxy-6-methyl-5,6,7,8-tetrahydro-[1,3]dioxolo[4,5-g]isoquinolin-5-yl)-1-(o-tolyl)ethan-1-one (3h). Following general procedure GP-3A, **3h** (634 mg, 90%) was obtained from **1** and **2h** as white solid [alternatively, following GP-3B, **3h** (80%) was obtained from **7b** and **2h**]. Mp: 89 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.63 (d, J = 7.5 Hz, 1H), 7.33 (d, J = 6.9 Hz, 1H), 7.25 (t, J = 7.5 Hz, 2H), 6.28 (s, 1H), 5.85 (d, J = 0.9 Hz, 2H), 4.28 (dd, J = 9.0, 3.0 Hz, 1H), 3.26–2.99 (m, 3H), 3.98 (s, 3H), 2.84–2.71 (m, 2H), 2.51 (s, 3H), 2.39–2.32 (m, 1H), 2.24 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 203.6, 147.7, 140.2, 138.7, 137.9, 133.9, 131.6, 130.5, 127.9, 125.3, 121.9, 102.7, 100.5, 59.2, 55.3, 46.7, 44.0, 41.6, 23.2, 20.6; MS (ESI) *m/z* $[M+H]^+$ calcd for $C_{21}H_{24}NO_4$ 354.17, found 354.25.

1-(2-aminophenyl)-2-(4-methoxy-6-methyl-5,6,7,8-tetrahydro-[1,3]dioxolo[4,5-g]isoquinolin-5-yl)ethan-1-one (3i). Following general procedure GP-3A, **3i** (654 mg, 92%) was obtained from **1** and **2i** as white crystalline solid [alternatively, following GP-3B, **3i** (90%) was obtained from **7b** and **2i**]. Mp: 128 °C; ^{1}H NMR (300 MHz ; $CDCl_3$): δ 7.84 (d, J = 8.1 Hz, 2H), 7.25 (d, J = 4.8 Hz, 1H), 6.66–6.62 (m, 2H), 6.32 (s, 3H), 5.85 (d, J = 1.8 Hz, 1H), 4.49 (dd, J = 7.8, 3.6 Hz, 1H), 3.95 (s, 3H), 3.19–3.13 (m, 3H), 2.95–2.75 (m, 2H), 2.47–2.45 (m, 1H), 2.40 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 201.5, 150.8, 148.1, 140.6, 134.3, 134.2, 131.6, 128.4, 122.9, 118.7, 117.7, 116.0, 102.9, 100.8, 59.5, 55.5, 44.7, 44.5, 42.3, 24.0; MS (ESI) *m/z* $[M+H]^+$ calcd for $C_{20}H_{23}N_2O_4$ 355.16, found 355.24.

2-(4-methoxy-6-methyl-5,6,7,8-tetrahydro-[1,3]dioxolo[4,5-g]isoquinolin-5-yl)-1-(3-nitrophenyl)ethan-1-one (3j). Following general procedure GP-3A, **3j** (694 mg, 90%) was obtained from **1** and **2j** as yellow solid [alternatively, following GP-3B, **3j** (85%) was obtained from **7b** and **2j**]. Mp: 113 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.86 (t, J = 0.6 Hz, 1H), 8.42–8.39 (m, 1H), 8.34–8.31 (m, 1H), 7.69 (t, J = 8.1 Hz, 1H), 5.86 (s, 2H), 6.31 (s, 1H), 4.38–4.34 (m, 1H), 4.04 (s, 3H), 3.38–3.32 (m, 1H), 3.23–3.12 (m, 2H), 2.92–2.74 (m, 2H), 2.43–2.37 (m, 1H), 2.32 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 197.0, 148.3, 148.0, 140.1, 138.4, 133.7, 128.0, 127.0, 123.3, 121.1, 102.8, 100.6, 59.4, 55.8, 44.1, 41.9, 23.1; MS (ESI) *m/z* $[M+H]^+$ calcd for $C_{20}H_{23}N_2O_6$ 370.16, found 370.17.

2-(4-methoxy-6-methyl-5,6,7,8-tetrahydro-[1,3]dioxolo[4,5-g]isoquinolin-5-yl)-1-(3-methoxyphenyl)ethan-1-one (3k). Following general procedure GP-3A, **3k** (674 mg, 91%) was obtained from **1** and **2k** as brownish white solid [alternatively, following GP-3B, **3k** (83%) was obtained from **7b** and **2k**]. Mp: 128 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.59–7.55 (m, 2H), 7.37–7.31 (m, 1H), 7.08 (d, J = 8.1 Hz, 1H), 6.29 (s, 1H), 5.83 (d, J = 1.2 Hz, 2H), 4.47 (t, J = 6.3 Hz, 1H), 3.94 (s, 3H), 3.83 (s, 3H), 3.19–3.08 (m, 3H), 2.91–2.71 (m, 2H), 2.44–2.41 (m, 1H), 2.35 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 198.7, 159.7, 147.8, 140.2, 138.6, 133.8, 129.4, 128.0, 122.1, 120.8, 119.1, 112.6, 102.6, 100.5, 59.1, 55.4, 55.1, 44.3, 43.7, 41.9, 23.6; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{21}H_{24}NO_5$ 370.1654, found 370.1649.

1-(3-aminophenyl)-2-(4-methoxy-6-methyl-5,6,7,8-tetrahydro-[1,3]dioxolo[4,5-g]isoquinolin-5-yl)ethan-1-one (3l). Following general procedure GP-3A, **3l** (661 mg, 93%) was obtained from **1** and **2l** as white solid. Mp: 158 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.39–7.19 (s, 1H), 6.85–6.83 (s, 1H), 6.30 (s, 1H), 5.84 (s, 2H), 4.47–4.45 (m, 1H), 3.93 (s, 3H), 3.18–3.08 (m, 3H), 2.87–2.73 (m, 2H), 2.47–2.42 (m, 1H), 2.36 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 199.0, 147.7, 146.6, 140.2, 138.4, 133.8, 129.3, 128.0, 122.4, 119.2, 118.7, 114.3, 102.5, 100.4, 59.1, 54.9, 44.4, 43.6, 41.9, 23.8; MS (ESI) *m/z* $[M+H]^+$ calcd for $C_{20}H_{23}N_2O_4$ 355.16, Found 355.17.

1-(5-bromo-2-hydroxyphenyl)-2-(4-methoxy-6-methyl-5,6,7,8-tetrahydro-[1,3]dioxolo[4,5-g]isoquinolin-5-yl)ethan-1-one (3m). Following general procedure GP-3A, **3m** (810 mg, 93%) was obtained from **1** and **2m** as white solid. Mp: 125 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.01 (d, J = 2.1 Hz, 1H),7.54 (dd, J = 6.3, 1.5 Hz, 1H), 6.91 (d, J = 8.4 Hz, 1H), 6.32 (s, 1H), 5.87 (s, 2H), 4.38 (dd, J = 5.7, 3.3 Hz, 1H), 4.05 (s, 3H), 3.28–3.05 (m, 3H), 2.94–2.76 (m, 2H), 2.47–2.40 (m, 1H), 2.38 (s, 3H);^{13}C NMR (75 MHz, $CDCl_3$): δ 204.9, 161.9, 140.5, 139.0, 134.0, 133.0, 128.4, 121.4, 121.3, 120.9, 110.7, 103.0, 100.9, 59.6, 56.5, 44.6, 44.3, 42.3, 23.5; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{20}H_{21}BrNO_5$ 434.0603, 436.0582 found 434.0598, 436.0580.

1-(2,4-dichlorophenyl)-2-(4-methoxy-6-methyl-5,6,7,8-tetrahydro-[1,3]dioxolo[4,5-g]isoquinolin-5-yl)ethan-1-one (3n). Following general procedure GP-3A, **3n** (745 mg, 91%) was obtained from **1** and **2n** as white crystalline solid. Mp: 96 °C; ^{1}H NMR(300 MHz, $CDCl_3$): δ 7.48–7.41 (m, 2H), 7.31–7.25 (m, 2H), 6.27 (s, 1H), 5.85 (s, 2H), 4.17–4.12 (m, 1H), 3.98 (s, 3H), 3.37–3.30 (m, 1H), 3.13–3.03 (m, 2H), 2.89–2.64 (m, 2H), 2.38–2.31 (m, 1H), 2.25 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 199.1, 145.7, 138.0, 135.9, 134.3, 131.6, 129.6, 128.4, 127.8, 125.8, 124.8, 119.0, 100.4, 98.3, 57.0, 53.0, 45.4, 41.8, 39.4, 20.8; MS (ESI) *m/z* $[M+H]^+$ calcd for $C_{20}H_{20}Cl_2NO_4$ 408.08, found 408.09.

1-(2,5-dichlorophenyl)-2-(4-methoxy-6-methyl-5,6,7,8-tetrahydro-[1,3]dioxolo[4,5-g]isoquinolin-5-yl)ethan-1-one (3o). Following general procedure GP-3A, **3o** (745 mg, 91%) was obtained from **1** and **2o** as grey white solid. Mp: 87 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.48 (s, 1H), 7.32 (s, 2H), 6.27 (s, 1H), 5.85 (s, 2H),4.15 (dd, J = 6.0, 3.9 Hz, 1H), 4.00 (s, 3H), 3.37–3.13 (m, 1H), 3.12–3.02 (m, 2H), 2.89–2.64 (m, 2H), 2.38–2.31 (m, 1H), 2.26 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 201.0, 147.9, 140.8, 140.1, 133.7, 132.6, 131.3, 130.9, 129.4, 128.9, 128.0, 120.9, 102.6, 100.5, 59.2, 55.2, 47.5, 44.0, 41,6, 22.9; MS (ESI) *m/z* $[M+H]^+$ calcd for $C_{20}H_{20}Cl_2NO_4$ 408.08 found 408.08.

1-(3,4-dichlorophenyl)-2-(4-methoxy-6-methyl-5,6,7,8-tetrahydro-[1,3]dioxolo[4,5-g]isoquinolin-5-yl)ethan-1-one (3p). Following general procedure GP-3A, **3p** (729 mg, 89%) was obtained from **1** and **2p** as white flake solid. Mp: 106 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.11–8.03 (m, 1H), 7.84–7.81 (m, 1H), 7.56–7.52 (m, 1H), 6.30 (s, 1H), 5.86 (s, 2H), 4.36 (dd, J = 8.7, 3.6 Hz, 1H), 3.99 (s, 3H), 3.23–3.06 (m, 2H), 2.92–2.73 (m, 2H), 2.43–2.36 (m, 1H), 2.33 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 196.9, 147.9, 140.1, 137.1, 136.7, 133.7, 132.9, 130.6, 130.4, 130.3, 128.0, 127.3, 121.4, 102.7, 100.5, 59.2, 55.4, 44.2, 43.9, 41.8, 26.6, 23.2; MS (ESI) *m/z* $[M+H]^+$ calcd for $C_{20}H_{20}Cl_2NO_4$ 408.08, found 408.10.

1-(5-chloro-2,4-dimethoxyphenyl)-2-(4-methoxy-6-methyl-5,6,7,8-tetrahydro-[1,3]dioxolo[4,5-g]isoquinolin-5-yl)ethan-1-one (3q). Following general procedure GP-3A, **3q** (807 mg, 93%) was obtained from **1** and **2q** as white solid. Mp : 180 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.85 (s, 1H), 6.45 (s, 1H), 6.29 (s, 1H), 5.84 (s, 2H), 4.47–4.43 (m, 1H), 3.95 (s, 3H), 3.91 (s, 3H), 3.88 (s, 3H), 3.35–3.26 (m, 1H), 3.10–3.00 (m, 2H), 2.91–2.80 (m, 1H), 2.74–2.68 (m, 1H), 2.45–2.39 (m, 1H), 2.36 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 197.8, 158.9, 158.4, 147.5, 140.3, 133.9, 132.3, 128.1, 122.9,

121.7, 114.2, 102.5, 100.4, 95.9, 59.1, 56.3,55.9, 54.4, 47.7, 44.7, 41.9, 24.3; MS (ESI) *m/z* $[M+H]^+$ calcd for $C_{22}H_{25}ClNO_6$ 434.14, found 434.15.

1-(2-hydroxy-3-methyl-4-nitrophenyl)-2-(4-methoxy-6-methyl-5,6,7,8-tetrahydro-[1,3]dioxolo[4,5-g]isoquinolin-5-yl)ethan-1-one (3r). Following general procedure GP-3A, **3r** (748 mg, 90%) was obtained from **1** and **2r** as grey solid [alternatively, following GP-3B, **3r** (85%) was obtained from **7b** and **2r**]. Mp: 145 °C; ^{1}H NMR (300 MHz, $CDCl_3$): *δ* 8.76 (s, 1H), 8.21 (s, 1H), 6.32 (s, 1H), 5.87 (s, 2H), 4.39–4.34 (m, 1H), 4.09 (s, 3H), 3.43–3.37 (m, 1H), 3.26–3.13 (m, 2H), 2.93–2.74 (m, 2H), 2.47–2.40 (m, 1H), 2.35 (s, 3H), 2.34 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): *δ* 205.2, 166.4, 148.1, 140.1, 138.6, 133.6, 130.5, 129.4, 127.9, 124.6, 120.5, 117.8, 102.6, 100.5, 59.3, 56.5, 44.1, 41.9, 22.8, 15.8; MS (ESI) *m/z* $[M+H]^+$ Calcd for $C_{21}H_{23}N_2O_7$ 415.15, found 415.34; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{21}H_{23}N_2O_7$ 415.1505, found 415.1500.

1-(2,4-dimethoxy-5-methylphenyl)-2-(4-methoxy-6-methyl-5,6,7,8-tetrahydro-[1,3]dioxolo[4,5-g]isoquinolin-5-yl)ethan-1-one (3s). Following general procedure GP-3A, **3s** (771 mg, 93%) was obtained from **1** and **2s** as white solid. Mp: 155 °C; ^{1}H NMR (300 MHz, $CDCl_3$): *δ* 7.63 (s, 1H), 6.36 (s, 1H), 6.29 (s, 1H), 5.84 (s, 2H), 4.55 (dd, *J* = 6.0, 2.1 Hz, 1H), 3.89 (s, 3H), 3.85 (s, 3H), 3.48–3.34 (m, 2H), 3.10–2.99 (m, 2H), 2.93–2.82 (m, 1H), 2.74–2.68 (m, 1H), 2.47–2.45 (m, 1H), 2.38(s, 3H), 2.14 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): *δ* 198.7, 161.7, 159.0, 147.4, 140.4, 133.9, 132.8, 128.0, 123.5, 120.3, 118.5, 102.4, 100.4, 94.2, 59.1, 55.7, 55.4, 54.1, 47.5, 44.8, 42.0, 24.6, 15.2; MS (ESI) *m/z* $[M+H]^+$ calcd for $C_{23}H_{28}NO_6$ 414.19, found 414.06.

2-(4-methoxy-6-methyl-5,6,7,8-tetrahydro-[1,3]dioxolo[4,5-g]isoquinolin-5-yl)-1-(2,4,6-trimethoxyphenyl)ethan-1-one (3t). Following general procedure GP-3A, **3t** (809 mg, 94%) was obtained from **1** and **2t** as white flake solid. Mp: 160 °C; ^{1}H NMR (300 MHz, $CDCl_3$): *δ* 6.25 (s, 1H), 6.08 (s, 2H), 5.83 (d, *J* = 2.4 Hz, 2H), 4.45 (dd, *J* = 8.7, 1.8 Hz, 1H), 3.92 (s, 3H), 3.81 (s, 3H), 3.77 (s, 6H), 3.20–2.97 (m, 2H), 2.92–2.42 (m, 3H), 2.45–2.41 (m, 1H), 2.38 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): *δ* 201.7, 162.0, 158.3, 147.4, 140.1, 133.8, 128.0, 123.1, 113.5, 102.3, 100.3, 90.4, 59.0, 55.7, 55.3, 53.6, 48.6, 41.7, 41.8, 24.8; MS (ESI) *m/z* $[M+H]^+$ calcd for $C_{23}H_{28}NO_7$ 430.19, found 430.23.

2-(4-methoxy-6-methyl-5,6,7,8-tetrahydro-[1,3]dioxolo[4,5-g]isoquinolin-5-yl)-1-(thiophen-2-yl)ethan-1-one (3aa). Following general procedure GP-3A, **3aa** (616 mg, 89%) was obtained from **1** and **2aa** as white solid [alternatively, following GP-3B, **3aa** (83%) was obtained from **7b** and **2aa**]. Mp: 114 °C; ^{1}H NMR (300 MHz, $CDCl_3$): *δ* 7.72 (d, *J* = 3.0 Hz, 1H), 7.59 (d, *J* = 4.5 Hz, 1H), 7.09 (t, *J* = 3.9 Hz, 1H), 6.28 (s, 1H), 5.82 (d, *J* = 1.2 Hz, 2H), 4.48 (dd, *J* = 8.4, 3.6 Hz, 1H), 3.93 (s, 3H), 3.22–3.04 (m, 3H), 2.91–2.71 (m, 2H), 2.44–2.42 (m, 1H), 2.38 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): *δ* 191.7, 147.8, 144.9, 140.1, 133.7, 133.2, 131.6, 128.0, 128.0, 122.0, 102.5, 100.4, 59.1, 55.4, 44.5, 44.1, 41.9, 23.8; MS (ESI) *m/z* $[M+H]^+$ calcd for $C_{18}H_{20}NO_4S$ 346.11, found 346.16.

1-(furan-2-yl)-2-(4-methoxy-6-methyl-5,6,7,8-tetrahydro-[1,3]dioxolo[4,5-g]isoquinolin-5-yl)ethan-1-one (3ab). Following general procedure GP-3A, **3ab** (594 mg, 90%) was obtained from **1** and **2ab** as white flakes [alternatively, following GP-3B, **3ab** (81%) was obtained from **7b** and **2ab**]. Mp: 99 °C; ^{1}H NMR (300 MHz, $CDCl_3$): *δ* 8.7 (t, *J* = 1.5 Hz, 1H), 7.56 (m, 1H), 7.18 (t, *J* = 3.3 Hz, 1H), 6.50 (t, *J* = 1.8 Hz, 1H), 6.3 (s, 1H), 5.84 (d, *J* = 1.2 Hz, 2H), 4.49 (dd, *J* = 6.6, 3.9 Hz, 1H), 3.93 (s, 3H), 3.20–3.12 (m, 2H), 2.99–2.71 (m, 3H), 2.79–2.57 (m, 1H), 2.48–2.45 (m, 1H), 2.39 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): *δ* 187.8, 153.0, 147.7, 146.0, 140.1, 133.7, 127.9, 122.0, 116.7, 112.0, 102.5, 100.4, 59.0, 55.0, 44.4, 43.0, 41.9, 23.8; MS (ESI) *m/z* $[M+H]^+$ calcd for $C_{18}H_{20}NO_5$ 330.13, found 330.21.

2-(4-methoxy-6-methyl-5,6,7,8-tetrahydro-[1,3]dioxolo[4,5-g]isoquinolin-5-yl)-1-(pyridin-3-yl)ethan-1-one (3ac). Following general procedure GP-3A, **3ac** (635 mg, 93%) was obtained from **1** and **2ac** as white solid [alternatively, following GP-3B, **3ac** (85%) was obtained from **7b** and **2ac**]. Mp: 138 °C; ^{1}H NMR (300 MHz, $CDCl_3$): *δ* 9.21 (s, *J* = 1.8 Hz, 1H), 8.76–8.75 (m, 1H), 8.28–8.25 (m, 1H), 7.43–7.39 (m, 1H), 6.31 (s, 1H), 5.86 (s, 2H), 4.42–4.38 (m, 1H), 3.98 (s, 3H), 3.28–3.09 (m, 3H), 2.93–2.73 (m, 2H), 2.45–2.38 (m, 1H), 2.34 (s, 3H); ^{13}C NMR (75MHz, $CDCl_3$): *δ* 197.9, 153.1, 149.8, 147.9, 140.1, 135.6, 133.7, 132.5, 128.0, 123.5, 121.5, 102.6, 100.5, 59.2, 55.2, 44.3, 44.0, 41.8, 23.3; MS (ESI) *m/z* $[M+H]^+$ calcd for $C_{19}H_{21}N_2O_4$ 341.15, found 341.23.

2-(4-methoxy-6-methyl-5,6,7,8-tetrahydro-[1,3]dioxolo[4,5-g]isoquinolin-5-yl)-1-(10H-phenothiazin-1-yl)ethan-1-one (3ad). Following general procedure GP-3A, **3ad** (766 mg, 83%) was obtained from **1** and **2ad** as brown solid. Mp: 158-160 °C;^{1}H NMR (300 MHz, $CDCl_3$): *δ* 7.44 (d, *J* = 8.0 Hz, 1H), 7.17 (s, 1H), 7.01–6.93 (m, 3H), 6.84 (t, *J* = 7.5 Hz, 1H), 6.56 (d, *J* = 7.5 Hz, 1H), 6.3 (s, 1H), 5.98 (s, 1H), 5.85 (d, *J* = 0.9 Hz, 2H), 4.44 (dd, *J* = 8.1, 4.5 Hz, 1H), 3.93 (s, 3H), 3.19–3.05 (m, 3H), 2.95–2.73 (m, 2H), 2.52–2.41 (m, 1H), 2.37 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): *δ* 198.5, 147.8, 141.9, 141.1, 140.1, 136.4, 133.7, 127.9, 127.7, 126.5, 126.1, 124.8, 122.6, 122.5, 122.0, 116.8, 114.8, 113.3, 102.6, 100.5, 59.1, 55.5, 44.3, 43.5, 41.9, 26.5, 23.6; MS (ESI) *m/z* $[M+H]^+$ calcd for $C_{26}H_{25}N_2O_4S$ 461.15, found 461.15.

2-(4-methoxy-6-methyl-5,6,7,8-tetrahydro-[1,3]dioxolo[4,5-g]isoquinolin-5-yl)-1-(naphthalen-2-yl)ethan-1-one (3ae). Following general procedure GP-3A, **3ae** (648 mg, 83%) was obtained from **1** and **2ae** as off-white solid [alternatively, following GP-3B, **3ae** (90%) was obtained from **7b** and **2ae**]. Mp: 132 °C; ^{1}H NMR (300 MHz, $CDCl_3$): *δ* 8.52 (s, 1H), 8.12–8.09 (m, 1H), 7.95–7.86 (m, 3H), 7.61–7.51 (m, 2H), 6.33 (s, 1H), 5.86 (d, *J* = 5.7 Hz, 2H), 4.55 (t, *J* = 6.0 Hz, 1H), 3.98 (s, 3H), 3.36 (d, *J* = 6.3 Hz, 2H), 3.25–3.15 (m, 1H), 2.95–2.34 (m, 2H), 2.48–2.42 (m, 1H), 2.38 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): *δ* 196.9, 145.8, 138.2, 133.4, 132.6, 131.8, 130.5, 127.8, 127.5, 126.2, 126.0, 125.7, 124.6, 122.3, 120.2, 100.6, 98.4, 57.2, 53.3, 42.4, 41.7, 39.9, 21.6; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{24}H_{24}NO_4$ 390.1705, found 390.1700.

1-(1-hydroxynaphthalen-2-yl)-2-(4-methoxy-6-methyl-5,6,7,8-tetrahydro-[1,3]dioxolo[4,5-g]isoquinolin-5-yl)ethan-1-one (3af). Following general procedure GP-3A, **3af** (740 mg, 91%) was obtained from **1** and **2af** as cement white solid. Mp: 147 °C; ^{1}H NMR (300 MHz, $CDCl_3$): *δ* 8.49 (d, *J* = 8.4 Hz, 1H), 7.81 (m, 2H), 7.64 (t, *J* = 6.3 Hz, 2H), 7.54 (t, *J* = 7.2 Hz, 1H), 7.25 (t, *J* = 4.5 Hz, 1H), 6.33 (s, 1H), 5.66 (d, *J* = 3.0 Hz, 2H), 4.54 (t, *J* = 6.0 Hz, 1H), 3.96 (s, 3H) 3.31–3.17 (m, 3H), 2.96–2.77 (m, 2H), 2.50–2.44 (m, 1H), 2.41 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): *δ* 205.1, 162.6, 147.9, 140.2, 137.2, 133.7, 129.8, 128.1, 127.3, 125.7, 125.4, 124.6, 124.4, 121.7, 118.0, 113.3, 102.6, 100.5, 59.1, 55.5, 44.4, 43.6, 41.9, 23.5; MS (ESI) *m/z* $[M+H]^+$ calcd for $C_{24}H_{24}NO_5$ 406.16, found 406.18.

1-(2-hydroxynaphthalen-1-yl)-2-(4-methoxy-6-methyl-5,6,7,8-tetrahydro-[1,3]dioxolo[4,5-g]isoquinolin-5-yl)ethan-1-one (3ag). Following general procedure GP-3A, **3ag** (723 mg, 89%) was obtained from **1** and **2ag** as grey flakes. Mp: 149 °C; ^{1}H NMR (300 MHz, $CDCl_3$): *δ* 7.89 (d, *J* = 8.7 Hz, 1H), 7.79–7.71 (m, 2H), 7.45–7.39 (m, 1H), 7.32–7.26 (m, 1H), 7.15–7.08 (m, 1H), 6.31 (s, 1H), 5.88 (d, *J* = 1.5 Hz, 2H), 4.68 (dd, *J* = 10.5, 2.7 Hz, 1H), 4.08 (s, 3H) 3.49–3.41 (m, 1H), 3.29–3.20 (m, 1H), 3.04–2.98 (m, 1H), 2.80–2.69 (m, 3H), 2.49 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): *δ* 205.4, 153.6, 145.9, 137.8, 131.8, 130.6, 128.6, 127.2, 125.9, 125.8, 125.7, 125.0, 122.0, 121.4, 121.0, 120.8, 119.0, 118.5, 117,5, 117.2, 99.9, 98.3, 57.1, 56.6, 47.6, 44.3, 40.4, 30.3, 21.7; MS (ESI) *m/z* $[M+H]^+$ calcd for $C_{24}H_{24}NO_5$ 406.16, found 406.23.

2-(4-methoxy-6-methyl-5,6,7,8-tetrahydro-[1,3]dioxolo[4,5-g]isoquinolin-5-yl)-1-(6-methoxynaphthalen-2-yl)ethan-1-one (3ah). Following general procedure GP-3A, **3ah** (757 mg, 90%) was obtained from **1** and **2ah** as white solid. Mp: 138 °C; ^{1}H NMR (300 MHz, $CDCl_3$): *δ* 8.45 (s, 1H), 8.10–8.06 (m, 1H), 7.84–7.75 (m, 2H),

7.21–7.16 (m, 2H), 6.33 (s, 1H), 5.86 (s, 2H), 4.55–4.51 (m, 1H), 3.97 (s, 3H), 3.94 (s, 3H), 3.32–3.00 (m, 2H), 3.24–3.15 (m, 1H), 2.95–2.74 (m, 2H), 2.48–2.42 (m, 1H), 2.38 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 198.5, 159.5, 147.7, 140.2, 137.1, 133.8, 132.7, 131.1, 129.7, 128.0, 127.8, 126.9, 125.0, 122.4, 119.5, 105.7, 102.6, 100.4, 59.2, 55.5, 55.2, 50.8, 44.4, 43.5, 41.9, 23.7; MS (ESI) *m/z* $[M+H]^+$ calcd for $C_{25}H_{26}NO_5$ 420.18, found 420.18.

1-(4,7-dimethoxybenzofuran-5-yl)-2-(4-methoxy-6-methyl-5,6,7,8-tetrahydro-[1,3]dioxolo[4,5-g]isoquinolin-5-yl)ethan-1-one (3ai). Following general procedure GP-3A, **3ai** (793 mg, 90%) was obtained from **1** and **2ai** as white flake [alternatively, following GP-3B, **3ai** (75%) was obtained from **7b** and **2ai**]. Mp: 167 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.61 (d, *J* = 1.8 Hz, 1H), 2.38 (s, 3H), 7.22 (s, 1H), 6.93 (d, *J* = 2.1 Hz, 1H), 6.30 (s, 1H), 5.84 (s, 2H), 4.51 (dd, *J* = 5.4, 2.7 Hz, 1H), 4.06 (s, 3H), 4.06 (s, 3H), 3.93 (s, 3H), 3.48–3.43 (m, 1H), 3.41–3.24 (m, 1H), 3.10–3.04 (m, 1H), 2.88–2.85 (m, 1H), 2.77–2.69 (m, 1H), 2.45–2.44 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 200.2, 147.7, 147.6, 144.9, 141.5, 140.3, 134.0, 128.1, 125.9, 122.8, 121.2, 107.4, 105.7, 102.5, 100.4, 61.5, 59.1, 56.3, 54.6, 47.7, 44.6, 41.9, 24.0; MS (ESI) *m/z* $[M+H]^+$ calcd for $C_{24}H_{26}NO_7$ 440.17, found 440.21.

1,3-bis(4-methoxy-6-methyl-5,6,7,8-tetrahydro-[1,3]dioxolo[4,5-g]isoquinolin-5-yl)propan-2-one (3aj). Following general procedure GP-3A, **3aj** (437 mg, 92%) was obtained from **1** and **2aj** (in excess) as grey solid. Mp: 168 °C; ^{1}H NMR (300MHz, $CDCl_3$): δ 6.30 (s, 2H), 5.86 (s, 4H), 4.43 (d, *J* = 9.9 Hz, 1H), 4.00 (s, 6H), 3.17–3.09 (m, 2H), 2.92–2.83 (m, 4H), 2.77–2.59 (m, 4H), 2.43 (s, 6H), 2.39–2.33 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 208.4, 147.6, 140.3, 133.8, 127.8, 122.2, 121.9, 102.7, 100.4, 59.1, 54.7, 48.6, 47.3, 47.0, 44.2, 43.7, 41.7, 41.5, 22.9; MS (ESI) *m/z* $[M+H]^+$ calcd for $C_{27}H_{33}N_2O_7$ 497.23, found 497.19.

3-acetyl-3-(4-methoxy-6-methyl-5,6,7,8-tetrahydro-[1,3]dioxolo[4,5-g]isoquinolin-5-yl)-6-methyl-2H-pyran-2,4(3H)-dione (3ak). Following general procedure GP-3A, **3ak** (707 mg, 91%, inseparable *dr* = 9:1) was obtained from **1** and **2ak** as white solid. Mp: 117 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.30 (s, 1H), 5.86 (s, 2H), 5.73 (s, 1H), 4.79–4.76 (m, 1H), 3.94 (s, 3H), 3.80–3.71 (m, 1H), 3.46 (s, 3H), 3.14–2.93 (m, 3H), 2.67 (s, 3H), 2.13 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 200.6, 181.9, 164.5, 163.7, 148.5, 140.0, 134.1, 126.0, 119.2, 105.2, 102.5, 102.2, 101.3, 100.7, 59.2, 55.2, 50.7, 45.0, 44.7, 41.0, 23.1, 20.1; MS (ESI) *m/z* $[M+H]^+$ calcd for $C_{20}H_{22}NO_7$ 388.14, found 388.12.

2-(4-methoxy-6-methyl-5,6,7,8-tetrahydro-[1,3]dioxolo[4,5-g]isoquinolin-5-yl)cyclopentane-1,3-dione (3am). Following general procedure GP-3A, **3am** (579 mg, 91%) was obtained from **1** and **2am** as white solid. Mp: 156 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.33 (s, 1H), 5.89–5.86 (m, 2H), 5.07 (s, 1H), 3.79 (s, 3H), 3.73 (m, 1H), 3.25–3.11 (m, 1H), 3.02–2.71 (m, 5H), 2.16 (s, 3H), 2.13 (s, 1H); ^{13}C NMR (75 MHz, DMSO–d_6): δ 198.4, 147.4, 135.0, 125.8, 109.1, 101.0, 100.8, 66.9, 65.5, 58.9, 49.2, 47.1, 36.6, 35.8, 34.8, 30.3; MS (ESI) *m/z* $[M+H]^+$ calcd for $C_{17}H_{20}NO_5$ 318.13, found 318.25.

2-(4-methoxy-6-methyl-5,6,7,8-tetrahydro-[1,3]dioxolo[4,5-g]isoquinolin-5-yl)cyclohexane-1,3-dione (3al). Following general procedure GP-3A, **3al** (598 mg, 90%) was obtained from **1** and **2al** as white solid [alternatively, following GP-3B, **3al** (82%) was obtained from **7b** and **2al**]. Mp: 187 °C; ^{1}H NMR (300 MHz, DMSO–D_6): δ 6.27 (s, 1H), 5.89–5.83 (m, 2H), 5.21 (m, 2H), 3.33–3.26 (m, 2H), 2.86–2.76 (m, 1H), 2.71–2.66 (m, 1H), 2.62 (s, 3H), 2.41–2.22 (m, 5H), 1.90–1.81 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 189.6, 148.0, 140.9, 135.9, 126.6, 120.9, 110.5, 102.0, 100.9, 59.5, 59.0, 51.2, 41.5, 34.7, 28.4, 20.6; MS (ESI) *m/z* $[M+H]^+$ calcd for $C_{17}H_{19}NO_5$ 332.15, found 332.16.

2-(4-methoxy-6-methyl-5,6,7,8-tetrahydro-[1,3]dioxolo[4,5-g]isoquinolin-5-yl)-1H-indene-1,3(2H)-dione (3an). Following general procedure GP-3A, **3an** (681 mg, 93%) was obtained from **1** and **2an** as solid. Mp: 188 °C; ^{1}H NMR (300 MHz, DMSO–D_6): δ 9.27 (s, 1H),7.28–7.25 (m, 2H),7.11–7.09 (m, 2H), 6.52 (s, 1H), 5.93 (s, 2H), 5.21 (s, 1H), 3.57 (s, 3H), 3.56–3.55 (s, 1H), 3.22–3.17 (m, 1H), 2.98–2.96 (m, 2H), 2.54 (s, 3H); ^{13}C NMR (75 MHz, DMSO–D_6): δ 189.0, 147.6, 139.7, 134.8, 129.5, 125.7, 117.3, 108.6, 101.9, 100.8, 59.1, 54.4, 48.9, 46.8, 34.0, 31.1, 26.5; MS (ESI) *m/z* $[M+H]^+$ calcd for $C_{21}H_{20}NO_5$ 366.13, found 366.15.

3-(4-methoxy-6-methyl-5,6,7,8-tetrahydro-[1,3]dioxolo[4,5-g]isoquinolin-5-yl)benzofuran-2(3H)-one (3ao). Following general procedure GP-3A, **3ao** (659 mg, 93%, inseparable *dr* = 85: 15) was obtained from **1** and **2ao** as white solid [alternatively, following GP-3B, **3ao** (90%, inseparable *dr* = 85: 15) was obtained from **7b** and **2ao**]. Mp:158-160 °C; ^{1}H (300 MHz,$CDCl_3$): δ 7.20 (d, *J* = 7.8 Hz, 1H), 7.07 (d, *J* = 8.1 Hz, 1H), 6.90–6.84 (m, 1H), 6.33 (s, 1H), 6.25 (s, 1H), 5.95 (d, *J* = 6.3 Hz, 2H), 4.51 (d, *J* = 4.5 Hz, 1H), 4.42 (d, *J* = 4.5 Hz, 1H), 4.07 (s, 1H), 3.63 (s, 1H), 2.86–2.80 (m, 1H), 2.43 (s, 3H), 2.30–2.24 (m, 1H), 2.05–2.00 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ (Mixture of diastereomers): 176.2, 154.4, 148.4, 148.1, 133.8, 128.3, 124.9, 123.4, 117.4, 110.5, 102.5, 100.7, 60.0, 59.4, 49.1, 46.3, 44.1, 22.6; MS (ESI) *m/z* $[M+H]^+$ calcd for $C_{20}H_{20}NO_5$ 354.13, found 354.15.

3-(4-methoxy-6-methyl-5,6,7,8-tetrahydro-[1,3]dioxolo[4,5-g]isoquinolin-5-yl)indolin-2-one (3ap). Following general procedure GP-3A, **3ap** (636 mg, 90%, inseparable *dr* = 75: 25) was obtained from **1** and **2ap** as white solid. Mp: 167-169 °C; ^{1}H NMR (300 MHz; $CDCl_3$): δ 7.98 (s, 1H), 7.13 (d, *J* = 7.2 Hz, 1H), 6.82 (d, *J* = 7.5 Hz, 1H), 6.75 (d, *J* = 7.5 Hz, 1H), 6.34 (s, 1H), 6.19 (d, *J* = 7.5 Hz, 1H), 5.94 (d, *J* = 6.0 Hz, 2H), 4.59 (d, *J* = 4.5 Hz, 1H), 4.15 (d, 1H, *J* = 4.5 Hz), 4.06 (s, 3H), 3.55 (s, 1H), 2.95–2.78 (m, 1H), 2.74–2.66 (m, 1H), 2.44 (s, 3H), 2.11–2.04 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ (Mixture of diastereomers): 178.9, 148.1, 142.1, 140.6, 133.9, 130.9, 130.0, 128.8, 127.4, 124.9, 122.3, 121.6, 118.6, 109.5, 102.4, 100.6, 59.5, 59.4, 51.0, 46.4, 43.9, 22.7; MS (ESI) *m/z* $[M+H]^+$ calcd for $C_{20}H_{20}N_2O_4$ 353.15, Found 353.18.

2-(4-methoxy-6-methyl-5,6,7,8-tetrahydro-[1,3]dioxolo[4,5-g]isoquinolin-5-yl)naphtho[2,1-b]furan-1(2H)-one (3aq). Following general procedure GP-3A, **3aq** (744 mg, 92%, inseparable *dr* = 85: 15) was obtained from **1** and **2aq** as grey solid. Mp: 188 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.84 (d, *J* = 8.1 Hz, 1H), 8.03 (d, *J* = 9.0 Hz, 1H), 7.83–7.81 (m, 1H),7.68–7.63 (m, 1H), 7.47–7.42 (m, 1H), 7.23–7.20 (m, 1H), 6.39 (s, 1H), 5.90 (s, 2H), 5.09 (d, *J*= 3.0 Hz 1H), 4.53 (d, *J* = 2.7 Hz, 1H), 4.02 (s, 3H), 3.18–3.08 (m, 1H), 2.81–2.72 (m, 1H), 2.59–2.49 (m, 2H), 2.39 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 200.2, 148.1, 140.1, 133.6, 130.9, 129.6, 128.5, 125.0, 123.4, 117.4, 102.6, 100.6, 89.7, 59.5, 59.2, 47.9, 44.3, 24.4; MS (ESI) *m/z* $[M+H]^+$ calcd for $C_{24}H_{22}NO_5$ 404.15, found 404.13.

1-(2-bromo-6-hydroxyphenyl)-2-(4-methoxy-6-methyl-5,6,7,8-tetrahydro-[1,3]dioxolo[4,5-g]isoquinolin-5-yl)ethan-1-one (9a). Following general procedure GP-3B, **9a** (729 mg, 84%) was obtained from **7b** and **8a** as white solid. Mp= 106 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.70 (d, *J* = 8.4 Hz, 1H), 7.18 (s, 1H), 7.03(d, *J* = 8.4 Hz, 1H), 6.31 (s, 1H), 5.86 (s, 2H), 4.38 (t, *J* =6.0 Hz, 1H), 3.95 (s, 3H), 3.18–3.10 (m, 3H), 2.93–2.75 (m, 2H), 2.47–2.41 (m, 1H), 2.39(s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 205.2, 163.4, 148.4, 140.4 134.0, 131.5, 130.5, 128.4, 122.6, 122.0, 121.6, 119.2, 103.0, 100.9, 59.5, 56.1, 44.8, 44.0, 42.3, 23.8; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{20}H_{21}BrNO_5$ 434.0603, 436.0582, found 434.0598, 436.0580.

1-(4-fluoro-2-hydroxyphenyl)-2-(4-methoxy-6-methyl-5,6,7,8-tetrahydro-[1,3]dioxolo[4,5-g]isoquinolin-5-yl)ethan-1-one (9b). Following general procedure GP-3B, **9b** (641 mg, 86%) was obtained from **7b** and **8b** as white solid. Mp= 127 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.87–7.82 (m, 1H), 6.68–6.55 (m, 2H), 6.32 (s, 1H), 5.86 (s, 2H), 4.42 (dd, *J* = 6.3, 3.0 Hz, 1H), 3.96 (s, 3H), 3.20–3.09 (m, 3H), 2.94–2.75 (m, 2H), 2.47–2.45 (m, 1H), 2.39 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 204.1, 168.8, 165.4, 165.0, 148.0, 140.1, 133.7, 132.5 ,132.3, 128.1, 121.3, 117.0, 117.0, 107.0, 106.7, 105.1, 104.8, 102.6, 100.5, 59.1, 55.6, 44.4, 43.5, 41.9, 23.4; HRMS (ESI)

m/z $[M+H]^+$ calcd for $C_{20}H_{21}FNO_5$ 374.1404, 375.1437, found 374.1398, 375.1431.

1-(3,4-dichlorophenyl)-2-(4-methoxy-6-methyl-5,6,7,8-tetrahydro-[1,3]dioxolo[4,5-g]isoquinolin-5-yl)ethan-1-one (9c). Following general procedure GP-3B, **9c** (652 mg, 80%) was obtained from **7b** and **8c** as white solid. Mp: 106 °C; ^{1}H NMR (300 MHz, $CDCl_3$): *δ* 8.11–8.03 (m, 1H), 7.84–7.81 (m, 1H), 7.56–7.52 (m, 1H), 6.30 (s, 1H), 5.86 (s, 2H), 4.36 (dd, *J* = 8.7, 3.6 Hz, 1H), 3.99 (s, 3H), 3.23–3.06 (m, 2H), 2.92–2.73 (m, 2H), 2.43–2.36 (m, 1H), 2.33 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): *δ* 196.9, 147.9, 140.1, 137.1, 136.7, 133.7, 132.9, 130.6, 130.4, 130.3, 128.0, 127.3, 121.4, 102.7, 100.5, 59.2, 55.5, 44.2, 43.9, 41.8, 26.6, 23.2; MS (ESI) *m/z* $[M+H]^+$ calcd for $C_{20}H_{20}Cl_2NO_4$ 408.08, found 408.10.

2-(9-bromo-4-methoxy-6-methyl-5,6,7,8-tetrahydro-[1,3]dioxolo[4,5-g]isoquinolin-5-yl)-1-phenylethan-1-one (12a). Following general procedure GP-3B, **12a** (684 mg, 82%) was obtained from **11b** and **2a** as white solid [alternatively, following GP-3A, **12a** (650 mg, 78%) was obtained from **10** and **2a**]. Mp=151 °C; ^{1}H NMR (300 MHz, $CDCl_3$): *δ* 8.01 (d, *J* = 7.5 Hz, 1H), 7.55 (t, *J* = 7.5 Hz, 1H), 7.45 (t, *J* = 7.8 Hz, 2H), 5.96 (s, 2H), 4.51–4.47 (dd, *J* = 8.1, 4.2 Hz, 1H), 3.93 (s, 3H), 3.22–3.10 (m, 3H), 2.89–2.83 (m, 1H), 2.76–2.64 (m, 1H), 2.53–2.46 (m, 1H), 2.34 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): *δ* 198.9, 146.3, 140.0, 137.6, 134.5, 133.1, 128.9, 128.6, 127.4, 124.7, 101.2, 96.5, 59.7, 55.4, 44.5, 43.6, 42.1, 23.9; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{20}H_{21}BrNO_5$ 418.0652, 418.0633, found 418.0648, 420.0630.

2-(9-bromo-4-methoxy-6-methyl-5,6,7,8-tetrahydro-[1,3]dioxolo[4,5-g]isoquinolin-5-yl)-1-(3-nitrophenyl)ethan-1-one (12b). Following general procedure GP-3B, **12b** (776 mg, 84%) was obtained from **11b** and **2j** as yellowish white solid [alternatively, following GP-3A, **12b** (748 mg, 81%) was obtained from **10** and **2j**]. Mp=125 °C; ^{1}H NMR (300 MHz, $CDCl_3$): *δ* 8.46 (s, 1H),7.42–7.31 (m, 2H), 7.67 (t, *J* = 7.2 Hz, 1H), 5.97 (s, 2H), 4.40–4.36 (dd, *J* = 8.1, 4.2 Hz, 1H), 4.04 (s, 3H), 3.35–3.13 (m, 3H), 2.89–2.83 (m, 1H), 2.74–2.62 (m, 1H), 2.51–2.44 (m, 1H), 2.29 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): *δ* 196.6, 148.3, 146.1, 139.5, 138.3, 134.1, 133.9, 129.8, 127.1, 127.0, 123.2, 123.1, 100.9, 96.2, 59.4, 55.6, 43.9, 43.8, 41.6, 22.7; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{20}H_{20}BrN_2O_6$ 463.0505, 465.0484, found 463.0499, 465.0482.

1-(3-aminophenyl)-2-(9-bromo-4-methoxy-6-methyl-5,6,7,8-tetrahydro-[1,3]dioxolo[4,5-g]isoquinolin-5-yl)ethan-1-one (12c). Following general procedure GP-3B, **12c** (743 mg, 86%) was obtained from **11b** and **2l** as grey solid [alternatively, following GP-3A, **12c** (760 mg, 88%) was obtained from **10** and **2l**]. Mp=168 °C; ^{1}H NMR (300 MHz, $CDCl_3$): *δ* 7.38–7.29 (m, 2H),7.21–7.20 (m, 1H), 6.85–6.82 (m, 1H), 5.95 (s, 2H), 4.50–4.48 (dd, *J* = 8.1, 4.2 Hz, 1H), 3.92 (s, 9H), 3.48–3.37 (m, 1H), 3.22–3.04 (m, 3H), 2.88–2.81 (m, 1H), 2.69–2.65 (m, 1H), 2.53–2.45 (m, 1H), 2.34 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): *δ* 198.6, 146.6, 145.8, 139.6, 138.3, 134.2, 129.3, 127.0, 124.5, 119.3, 118.6, 114.2, 100.8, 96.1, 59.3, 55.0, 44.1, 43.2, 41.7, 23.6; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{20}H_{22}BrN_2O_4$ [433.0757, 435.0739, found 433.0755, 437.0736.

2-(9-bromo-4-methoxy-6-methyl-5,6,7,8-tetrahydro-[1,3]dioxolo[4,5-g]isoquinolin-5-yl)-1-(2-bromo-6-hydroxyphenyl)ethan-1-one (12d). Following general procedure GP-3B, **12d** (868 mg, 85%) was obtained from **11b** and **8a** as white solid [alternatively, following GP-3A, **12d** (907 mg, 89%) was obtained from **10** and **8a**]. Mp=133 °C; ^{1}H NMR (300 MHz, $CDCl_3$): *δ* 7.65 (d, *J* = 8.7 Hz, 1H), 7.18 (s, 2H), 7.00 (d, *J* = 7.8 Hz, 1H), 5.96 (s, 2H), 4.42–4.38 (dd, *J* = 8.1, 4.2 Hz, 1H), 3.94 (s, 3H), 3.19–3.09 (m, 3H), 2.91–2.84 (m, 1H), 2.76–2.60 (m, 1H), 2.53–2.46 (m, 1H), 2.36 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): *δ* 204.4, 163.0, 146.1, 139.4, 134.0, 131.0, 130.3, 127.0, 123.3, 122.3, 121.7, 118.6, 109.6, 100.9, 96.1, 59.3, 55.6, 44.0, 43.2, 41.7, 23.1; MS (ESI) *m/z* $[M+H]^+$ calcd for $C_{20}H_{20}Br_2NO_5$ 511.97, found 511.75.

2-(9-bromo-4-methoxy-6-methyl-5,6,7,8-tetrahydro-[1,3]dioxolo[4,5-g]isoquinolin-5-yl)-1-(3,4-dichlorophenyl)ethan-1-one (12e). Following general procedure GP-3B, **12e** (834 mg, 84%) was obtained from **11b** and **8c** as white solid [alternatively, following GP-3A, **12e** (824 mg, 85%) was obtained from **10** and **8c**]. Mp=140 °C; ^{1}H NMR (300 MHz, $CDCl_3$): *δ* 8.10 (s, 1H),7.84–7.81 (m, 2H), 7.56 (d, *J* = 5.4 Hz, 1H), 5.97 (s, 2H), 4.39–4.35 (dd, *J* = 8.1, 4.0 Hz, 1H), 3.19–3.09 (m, 3H), 3.99 (s, 3H), 2.90–2.83 (m, 1H), 2.74–2.62 (m, 1H), 2.51–2.44 (m, 1H), 2.31 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): *δ* 196.9, 146.4, 139.9, 137.6, 137.0, 134.5, 133.4, 131.1, 130.8, 127.7, 127.4, 123.9, 101.3, 96.6, 59.8, 55.9, 44.2, 44.0, 42.0, 23.3; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{20}H_{19}BrCl_2NO_4$ 485.9869, 487.9847, 489.9823, found 485.9867, 487.9844, 489.9822.

2-(9-bromo-4-methoxy-6-methyl-5,6,7,8-tetrahydro-[1,3]dioxolo[4,5-g]isoquinolin-5-yl)-1-(2,4,6-trimethoxyphenyl)ethan-1-one (12f). Following general procedure GP-3B, **12f** (851 mg, 84%) was obtained from **11b** and **2t** as white solid [alternatively, following GP-3A, **12f** (882 mg, 87%) was obtained from **10** and **2t**]. Mp=162 °C; ^{1}H NMR (300 MHz, $CDCl_3$): *δ* 7.26 (s, 2H), 5.96 (s, 2H), 4.50–4.48 (dd, *J* = 8.1, 4.1, Hz, 1H), 3.94 (s, 3H), 3.91 (s, 9H), 3.48–3.37 (m, 1H), 3.19–3.06 (m, 3H), 2.90–2.84 (m, 1H), 2.76–2.65 (m, 1H), 2.53–2.46 (m, 1H), 2.36 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): *δ* 197.6, 153.4, 146.3, 142.7, 140.0, 134.6, 132.8, 127.4, 124.6, 106.1, 101.2, 96.5, 61.3, 59.7, 56.7, 55.5 44.5, 43.5, 42.1, 23.8; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{23}H_{27}BrNO_7$ 508.0965, 510.0948, found 508.0964, 510.0948.

2-(9-bromo-4-methoxy-6-methyl-5,6,7,8-tetrahydro-[1,3]dioxolo[4,5-g]isoquinolin-5-yl)-1-(6-methoxynaphthalen-2-yl)ethan-1-one (12g). Following general procedure GP-3B, **12g** (854 mg, 86%) was obtained from **11b** and **2ah** as white solid [alternatively, following GP-3A, **12g** (884 mg, 89%) was obtained from **10** and **2ah**]. Mp=181 °C; ^{1}H NMR (300 MHz, $CDCl_3$): *δ* 8.43 (s, 1H), 8.08–8.05 (m, 1H), 7.84–7.76 (m, 2H), 7.20–7.16 (m, 2H), 5.96 (s, 2H), 4.58–4.54 (dd, *J* = 8.0, 4.2 Hz, 1H), 3.96 (s, 3H), 3.95 (s, 3H), 3.32–3.15 (m, 3H), 2.92–2.84 (m, 1H), 2.78–2.66 (m, 1H), 2.78–2.66 (m, 1H), 2.56–2.48 (m, 1H), 2.36 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): *δ* 198.1, 159.6, 145.9, 139.6, 137.1, 134.2, 132.6, 131.1, 129.6, 127.8, 127.0, 125.0, 124.4, 119.6, 105.7, 100.8, 96.1, 59.3, 55.4, 55.3, 44.1, 43.1, 41.7, 23.5; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{25}H_{25}BrNO_5$ 498.0911, 500.0894, found 498.0911, 500.0894.

2-(9-bromo-4-methoxy-6-methyl-5,6,7,8-tetrahydro-[1,3]dioxolo[4,5-g]isoquinolin-5-yl)-1-(1-hydroxynaphthalen-2-yl)ethan-1-one (12h). Following general procedure GP-3B, **12h** (821 mg, 85%) was obtained from **11b** and **2af** as grey solid. Mp=150 °C; ^{1}H NMR (300 MHz, $CDCl_3$): *δ* 8.43(s, 1H), 8.08–8.05 (m, 1H), 7.84–7.76 (m, 2H), 7.28 (s, 1H), 5.96 (s, 2H), 4.54–4.52 (dd, *J* = 8.1, 4.0 Hz, 1H), 3.95 (s, 3H), 3.30–3.20 (m, 3H), 2.94–2.87 (m, 1H), 2.78–2.67 (m, 1H), 2.57–2.49 (m, 1H), 2.39 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): *δ* 205.0, 163.0, 146.4, 139.9, 137.6, 134.4, 130.3, 127.8, 127.7, 127.5, 126.3, 126.2, 125.8, 125.3, 124.8, 124.2, 118.7, 118.5, 113.6, 101.2, 96.5, 59.6, 55.9, 44.4, 43.6, 42.1, 27.3, 23.7; MS (ESI) *m/z* $[M+H]^+$ calcd for $C_{24}H_{23}BrNO_5$ 484.08, found 484.20.

2-(9-bromo-4-methoxy-6-methyl-5,6,7,8-tetrahydro-[1,3]dioxolo[4,5-g]isoquinolin-5-yl)-1-(6-hydroxy-4,7-dimethoxybenzofuran-5-yl)ethan-1-one (12i). Following general procedure GP-3B, **12i** (895 mg, 84%) was obtained from **11b** and **5** as greenish solid [alternatively, following GP-3A, **12i** (970 mg, 91%) was obtained from **10** and **5**]. Mp=147 °C; ^{1}H NMR (300 MHz, $CDCl_3$): *δ* 7.49 (d, *J* = 2.1 Hz, 1H), 6.85 (d, *J* = 2.1 Hz, 1H), 5.95 (s, 2H), 4.55–4.51 (dd, *J* = 8.1, 4.1, Hz, 1H), 4.05 (s, 3H), 4.04 (s, 3H), 3.90 (s, 3H), 3.47–3.39 (m, 1H), 3.19–3.11 (m, 2H), 2.89–2.82 (m, 1H), 2.76–2.64 (m, 1H), 2.55–2.48 (m, 1H), 2.39 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): *δ* 205.5, 151.3, 151.0, 149.5, 145.9, 143.7, 139.6, 134.1, 129.3, 126.8, 123.8, 113.1, 111.2, 105.6, 100.8, 96.0, 61.1,

60.8, 59.2, 55.1, 48.4, 44.1, 41.4, 23.5; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{24}H_{24}BrNO_8$ 534.0758, 536.0741, found 534.0748, 536.0731.

2-(9-bromo-4-methoxy-6-methyl-5,6,7,8-tetrahydro-[1,3]dioxolo[4,5-g]isoquinolin-5-yl)cyclohexane-1,3-dione (12j). Following general procedure GP-3B, **12j** (670 mg, 82%) was obtained from **11b** and **2al** as white solid [alternatively, following GP-3A, **12j** (687 mg, 84%) was obtained from **10** and **2al**]. Mp=174 °C; ^{1}H NMR (300 MHz, $CDCl_3$): *δ* 5.98 (s, 2H), 5.17 (t, *J* = 3.6 Hz, 1H), 3.79 (s, 3H), 3.35–3.30 (m, 1H), 3.03–2.87 (m, 2H), 2.77–2.72 (m, 1H), 2.58 (s, 3H), 2.34–2.27 (m, 5H), 1.87–1.83 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): *δ* 189.8, 146.2, 140.1, 135.9, 125.9, 122.8, 110.4, 101.3, 95.2, 59.1, 58.9, 50.4, 41.3, 34.9, 27.6, 20.7; MS (ESI) *m/z* $[M+H]^+$ calcd for $C_{18}H_{21}BrNO_5$ 410.06, found 410.17.

2-(9-bromo-4-methoxy-6-methyl-5,6,7,8-tetrahydro-[1,3]dioxolo[4,5-g]isoquinolin-5-yl)-1-(furan-2-yl)ethan-1-one (12k). Following general procedure GP-3B, **12k** (718 mg, 88%) was obtained from **11b** and **2ab** as brown solid [alternatively, following GP-3A, **12k** (703 mg, 86%) was obtained from **10** and **2ab**]. Mp=102 °C; ^{1}H NMR (300 MHz, $CDCl_3$): *δ* 7.56 (d, *J* = 3.3 Hz, 1H), 7.18 (d, *J* = 3.3 Hz, 1H), 6.53–6.51 (m, 1H), 5.95 (s, 2H), 4.52–4.48 (dd, *J* = 8.0, 4.1 Hz, 1H), 3.23–3.07 (m, 2H), 3.90 (s, 3H), 2.94–2.84 (m, 2H), 2.77–2.64 (m, 1H), 2.53–2.46 (m, 1H), 2.37 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): *δ* 187.6, 153.0, 139.5, 134.1, 127.0, 124.1, 116.7, 112.1, 100.8, 96.0, 59.2, 55.0, 44.1, 42.7, 41.7, 23.7; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{18}H_{19}BrNO_5$ 408.0441, 410.0423, found 408.0438, 410.0419.

2-(9-bromo-4-methoxy-6-methyl-5,6,7,8-tetrahydro-[1,3]dioxolo[4,5-g]isoquinolin-5-yl)-1-(thiophen-2-yl)ethan-1-one (12l). Following general procedure GP-3B, **12l** (752 mg, 89%) was obtained from **11b** and **2aa** as grey solid [alternatively, following GP-3A, **12l** (736 mg, 87%) was obtained from **10** and **2aa**]. Mp=75 °C; ^{1}H NMR (300 MHz, $CDCl_3$): *δ* 7.73 (d, *J* = 4.2 Hz, 1H),7.62 (d, *J* = 3.9 Hz, 1H), 7.11 (t, *J* = 4.2 Hz, 1H), 5.96 (s, 2H), 4.53–4.48 (dd, *J* = 8.1, 4.0 Hz, 1H), 3.94 (s, 3H), 3.24–3.01 (m, 3H), 2.90–2.83 (m, 1H), 2.77–2.65 (m, 1H), 2.54–2.47 (m, 1H), 2.38 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): *δ* 191.3, 144.8, 139.5, 134.1, 133.2, 131.5, 127.9, 127.1, 124.1, 100.8, 96.0, 59.3, 55.4, 44.1, 43.8, 41.7, 23.6; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{18}H_{19}BrSNO_4$ 424.0213, 426.0193, found 424.0210, 426.0190.

2-(9-bromo-4-methoxy-6-methyl-5,6,7,8-tetrahydro-[1,3]dioxolo[4,5-g]isoquinolin-5-yl)-1-(pyridin-3-yl)ethan-1-one (12m). Following general procedure GP-3B, **12m** (652 mg, 78%) was obtained from **11b** and **2ac** as orange solid [alternatively, following GP-3A, **12m** (693 mg, 83%) was obtained from **10** and **2ac**]. Mp=236 °C; ^{1}H NMR (300 MHz, $CDCl_3$): *δ* 9.20 (s, 1H), 8.77 (d, *J* = 4.8 Hz, 1H), 8.28–8.24 (m, 1H), 7.44–7.40 (m, 1H), 5.95 (s, 2H), 4.45–4.41 (m, 1H), 3.97 (s, 3H), 3.21–3.09 (m, 3H), 2.90–2.83 (m, 1H), 2.76–2.62 (m, 1H), 2.52–2.45 (m, 1H), 2.32 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): *δ* 197.5, 153.2, 149.7, 146.0, 139.5, 135.6, 134.1, 132.4, 127.0, 123.6, 123.5, 100.9, 96.1, 59.3, 55.2, 43.9, 43.7, 41.6, 23.0; MS (ESI) *m/z* $[M+H]^+$ calcd for $C_{19}H_{20}BrN_2O_4$ 419.06, found 419.18.

3-(9-bromo-4-methoxy-6-methyl-5,6,7,8-tetrahydro-[1,3]dioxolo[4,5-g]isoquinolin-5-yl)isobenzofuran-1(3H)-one (12n). Following general procedure GP-3B, **12n** (732 mg, 85%, inseparable *dr* = 3:1) was obtained from **11b** and **2ao** as white solid. Mp: 137-139 °C; ^{1}H (300 MHz,$CDCl_3$): *δ* 7.22 (d, *J* = 7.8 Hz, 1H), 7.08 (d, *J* = 8.1 Hz, 1H), 6.88–6.83 (m, 1H), 6.39 (s, 1H), 6.03 (d, *J* = 6.3 Hz, 2H), 4.50 (d, *J* = 4.5 Hz, 1H), 4.05 (s, 1H), 3.60 (s, 1H), 2.86–2.79 (m, 1H), 2.40 (s, 3H), 2.33–2.29 (m, 1H), 2.05–2.13 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): *δ* (Mixture of diastereomers) Major: 176.2, 154.4, 148.4, 148.1, 133.8, 128.3, 124.9, 123.4, 117.4, 110.5, 102.5, 100.7, 60.0, 59.4, 49.1, 46.3, 44.1, 22.6; MS (ESI) *m/z* $[M+H]^+$ calcd for $C_{20}H_{19}BrNO_5$ 432.05, found 432.05.

4,7-dimethoxy-5-(2-(4-methoxy-6-methyl-5,6,7,8-tetrahydro-[1,3]dioxolo[4,5-g]isoquinolin-5-yl)acetyl)benzofuran-6-yl trifluoromethanesulfonate (16a). Following general procedure GP-3B, **16a** (880 mg, 75%) was obtained from **7b** and **5a** as colorless liquid. ^{1}H NMR (300 MHz, $CDCl_3$): *δ* 7.68 (s, 1H), 6.95 (s, 1H), 6.24 (s, 1H), 5.82 (s, 2H), 4.33 (d, *J* = 8.4 Hz, 1H), 4.19 (s, 3H), 4.01 (s, 3H), 3.96 (s, 3H), 3.30–3.21 (m, 1H), 3.10–3.04 (m, 2H), 2.89–2.69 (m, 2H), 2.29 (s, 3H), 2.35–2.32 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): *δ* 199.2, 148.1, 147.2, 146.6, 145.4, 140.7, 134.2, 134.1, 134.1, 128.6, 123.0, 122.0, 121.2, 121.2, 116.9, 105.7, 102.8, 100.8, 62.2, 61.4, 59.4, 54.6, 49.2, 44.3, 42.0, 23.6; MS (ESI) *m/z* $[M+H]^+$ calcd for $C_{25}H_{25}F_3NO_{10}S$ 588.12, found 588.22.

1-(6-(benzyloxy)-4,7-dimethoxybenzofuran-5-yl)-2-(4-methoxy-6-methyl-5,6,7,8-tetrahydro-[1,3]dioxolo[4,5-g]isoquinolin-5-yl)ethan-1-one (16b). Following general procedure GP-3B, **16b** (1.01 g, 93%) was obtained from **7b** and **5b** as colorless liquid. ^{1}H NMR (300 MHz, $CDCl_3$): *δ* 7.58 (d, *J* = 2.4 Hz, 1H), 7.51 (d, *J* = 6.6 Hz, 1H), 7.36–7.32 (m, 3H), 6.88 (d, *J* = 2.4 Hz, 1H), 6.24 (s, 1H), 5.80 (s, 2H), 5.13–5.03 (m, 2H), 4.55 (d, *J* = 8.7 Hz, 1H), 4.06 (s, 3H), 4.00 (s, 3H), 3.81 (s, 3H), 3.27–3.18 (m, 1H), 2.97–2.82 (m, 3H) 2.67–2.61 (m, 1H), 2.38–2.33 (m, 1H), 2.35 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): *δ* 201.8, 147.5, 147.5, 144.8, 144.5, 144.5, 140.1, 137.4, 134.7, 133.8, 128.5, 128.3, 128.1, 127.9, 124.7, 123.0, 116.8, 105.1, 102.3, 100.3, 61.3, 61.2, 59.0, 53.0, 49.0, 44.5, 41.9, 24.5; MS (ESI) *m/z* $[M+H]^+$ calcd for $C_{32}H_{32}NO_8$ 546.21, found 546.35.

2-(4-methoxy-6-methyl-5,6,7,8-tetrahydro-[1,3]dioxolo[4,5-g]isoquinolin-5-yl)-1-(4,6,7-trimethoxybenzofuran-5-yl)ethan-1-one (16c). Following general procedure GP-3B, **16c** (853 mg, 91%) was obtained from **7b** and **5c** as colorless liquid. ^{1}H NMR (300 MHz, $CDCl_3$): *δ* 7.56 (d, *J* = 2.4 Hz, 1H), 6.86 (d, *J* = 2.4 Hz, 1H), 6.26 (s, 1H), 5.83 (s, 2H), 4.59 (d, *J* = 8.8 Hz, 1H), 4.07 (s, 3H), 3.98 (s, 3H), 3.94 (s, 3H), 3.90 (s, 3H), 3.29–3.20 (m, 1H), 3.02–2.71 (m, 4H), 2.52–2.40 (m, 1H), 2.44 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): *δ* 201.7, 148.5, 147.5, 145.9, 144.5, 144.3, 140.1, 134.3, 133.9, 128.0, 124.2, 123.1, 116.6, 105.0, 102.3, 100.4, 62.4, 61.4, 61.0, 59.1, 52.9, 48.8, 44.8, 41.9, 25.0; MS (ESI) *m/z* $[M+H]^+$ calcd for $C_{25}H_{28}NO_4$ 470.18, found 470.25.

1-(6-butoxy-4,7-dimethoxybenzofuran-5-yl)-2-(4-methoxy-6-methyl-5,6,7,8-tetrahydro-[1,3]dioxolo[4,5-g]isoquinolin-5-yl)ethan-1-one (16d). Following general procedure GP-3B, **16d** (858 mg, 84%) was obtained from **7b** and **5d** as colorless liquid. ^{1}H NMR (300 MHz, $CDCl_3$): *δ* 7.55 (s, 1H), 6.85 (s, 1H), 6.25 (s, 1H), 5.83 (d, *J* = 4.5 Hz, 2H), 4.56 (d, *J* = 8.4 Hz, 1H), 4.12–4.03 (m, 2H), 4.04(s, 3H), 3.97 (s, 3H), 3.93 (s, 3H), 3.26–3.18 (m, 2H), 2.03–2.82 (m, 3H), 2.43 (s, 3H), 2.34–2.77 (m,1H), 1.74–1.67 (m, 2H), 1.48–1.41 (m, 2H), 0.95 (t, *J* = 7.2 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): *δ* 201.8, 148.6, 147.5, 145.4, 144.4, 140.1, 134.4, 133.9, 128.0, 124.6, 123.0, 116.3, 105.0, 102.3, 100.4, 75.1, 61.3, 61.0, 59.1, 53.0, 48.9, 44.6, 41.9, 32.2, 24.6, 19.1, 13.9; MS (ESI) *m/z* $[M+H]^+$ calcd for $C_{28}H_{34}NO_8$ 512.23, found 512.25.

1-(4,7-dimethoxy-6-(octyloxy)benzofuran-5-yl)-2-(4-methoxy-6-methyl-5,6,7,8-tetrahydro-[1,3]dioxolo[4,5-g]isoquinolin-5-yl)ethan-1-one (16e). Following general procedure GP-3B, **16e** (941 mg, 83%) was obtained from **7b** and **5e** as colorless liquid. ^{1}H NMR (300 MHz, $CDCl_3$): *δ* 7.55 (s, 1H), 6.86 (s, 1H), 6.26 (s, 1H), 5.82 (d, *J* = 4.5 Hz, 2H), 4.56 (d, *J* = 8.1 Hz, 1H), 4.06–4.01 (m, 2H), 4.05(s, 3H), 3.98 (s, 3H), 3.93 (s, 3H), 3.27–3.21 (m, 1H), 3.06–2.70 (m, 4H) 2.43 (s, 3H), 2.37–2.36 (m, 1H), 1.77–1.68 (m, 2H), 1.40–1.23 (m, 10H), 0.87 (t, *J* = 6.3 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): *δ* 201.8, 148.6, 147.5, 145.4, 144.4, 140.1, 134.4, 133.9, 128.0, 124.6, 123.0, 116.3, 105.0, 102.3, 100.3, 75.5, 61.3, 61.1, 59.1, 53.0, 48.9, 44.6, 41.9, 31.9, 30.1, 29.5, 29.3, 25.9, 24.7, 22.7, 14.1; MS (ESI) *m/z* $[M+H]^+$ calcd for $C_{32}H_{42}NO_8$ 568.29, found 568.23.

1-(6-(decyloxy)-4,7-dimethoxybenzofuran-5-yl)-2-(4-methoxy-6-methyl-5,6,7,8-tetrahydro-[1,3]dioxolo[4,5-g]isoquinolin-5-yl)ethan-1-one (16f). Following general procedure GP-3B, **16f** (952

mg, 80%) was obtained from **7b** and **5f** as colorless liquid. ^{1}H NMR (300 MHz, $CDCl_3$): *δ* 7.55 (s, 1H), 6.86 (s, 1H), 6.26 (s, 1H), 5.82 (d, *J* = 4.5 Hz, 2H), 4.56 (d, *J* = 8.1 Hz, 1H), 4.07–4.01 (m, 2H), 4.05 (s, 3H), 3.98 (s, 3H), 3.93 (s, 3H), 3.27–3.18 (m, 1H), 3.06–2.65 (m, 4H), 2.43 (s, 3H), 2.37–2.35 (m, 1H), 1.75–1.70 (m, 2H), 1.40–1.26 (m, 14H), 0.87 (t, *J* = 6.0 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 201.8, 148.6, 147.5, 145.4, 144.3, 140.1, 134.4, 133.9, 128.0, 124.6, 123.0, 116.3, 105.0, 102.3, 100.3, 75.5, 61.3, 61.0, 59.1, 53.0, 48.9, 44.6, 41.9, 31.9, 30.1, 29.6, 29.5, 29.3, 25.9, 24.7, 22.7, 14.1; MS (ESI) *m/z* $[M+H]^+$ calcd for $C_{34}H_{46}NO_8$ 596.32, found 596.41.

1-(6-hydroxy-4-methoxybenzofuran-5-yl)-2-(4-methoxy-6-methyl-5,6,7,8-tetrahydro-[1,3]dioxolo[4,5-g]isoquinolin-5-yl)ethan-1-one (16g). Following general procedure GP-3B, **16g** (747 mg, 88%) was obtained from **7b** and **14** as colorless liquid. ^{1}H NMR (300 MHz, $CDCl_3$): *δ* 7.43 (t, *J* = 2.4 Hz, 1H), 6.86 (d, *J* = 1.5 Hz, 1H), 6.75 (d, *J* = 1.5 Hz, 1H), 6.30 (s, 1H), 5.84 (s, 2H), 4.54 (d, *J* = 8.7 Hz, 1H), 4.06 (s, 3H), 4.12 (s, 3H), 3.90 (s, 3H), 3.48–3.40 (m, 1H), 3.23–3.07 (m, 2H), 2.94–2.74 (m, 2H), 2.50–2.44 (m, 1H), 2.41 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): *δ* 205.7, 162.2, 160.0, 159.8, 154.8, 147.8, 143.3, 143.1, 140.2, 133.8, 127.8, 122.0, 111.8, 109.7, 109.5, 105.7, 105.6, 102.5, 100.4, 94.5, 94.2, 60.2, 55.0, 48.9, 44.6, 41.7, 33.5, 23.8; MS (ESI) *m/z* $[M+H]^+$ calcd for $C_{23}H_{24}NO_7$ 426.16, found 426.26.

1-(1H-indol-5-yl)-2-(4-methoxy-6-methyl-5,6,7,8-tetrahydro-[1,3]dioxolo[4,5-g]isoquinolin-5-yl)ethan-1-one (16h). Following general procedure GP-3B, **16h** (680 mg, 90%) was obtained from **7b** and **15** as yellow liquid. ^{1}H NMR (300 MHz, $CDCl_3$): *δ* 8.90 (s, 1H), 8.38 (s, 1H), 7.92 (dd, *J* = 7.2, 1.5 Hz, 1H), 7.37 (t, *J* = 2.7 Hz, 1H), 7.24 (d, *J* = 2.7 Hz, 1H), 6.62 (d, *J* = 2.1 Hz, 1H), 5.86 (s, 2H), 6.32 (s, 1H), 4.61 (d, *J* = 8.7 Hz, 1H), 3.95 (s, 3H), 3.38–3.16 (m, 3H), 2.94–2.76 (m, 2H), 2.50–2.43 (m, 1H), 2.40 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): *δ* 205.7, 162.2, 160.0, 159.8, 154.8, 147.8, 143.3, 143.1, 140.2, 133.8, 127.8, 122.0, 111.8, 109.7, 109.5, 105.7, 105.6, 102.5, 100.4, 94.5, 94.2, 60.2, 55.0, 48.9, 44.6, 41.7, 33.5, 23.8; MS (ESI) *m/z* $[M+H]^+$ calcd for $C_{22}H_{23}N_2O_4$ 397.17, found 379.28.

2-methyl-1,2,3,4-tetrahydroisoquinoline (18). To 1,2,3,4-tetrahydroisoquinoline **17** (10 ml, 80 mmol) at 0 °C, formic acid (6.08 ml, 160 mmol) and 37% aqueous formaldehyde (6.64 ml, 88 mmol) were added dropwise for 15-20 min. The CO_2 gas evolved slowly as a result of reaction. The resulting gel was heated at 85 °C for overnight. The above mixture was cooled to 0 °C and then treated under stirring with a 6N HC1 solution (80 mL). The mixture was extracted with ethyl acetate (3 x 50 ml). The aqueous phase was made basic with 20% NaOH to adjust pH >10 and re-extracted with ethyl acetate (3 x 50 ml). The latter organic extracts were then combined, washed with brine, dried (Na_2SO_4) and concentrated *in vacuo* to yield the pure product **18** (9.96g, 85%) as a yellow oil. R_f = 0.5 (1:1 H_2O:MeOH); ^{1}H NMR (300 MHz, $CDCl_3$): *δ* 7.13–7.10 (m, 3H), 7.05–7.02 (m, 2H), 3.59 (s, 2H), 2.93 (t, *J* = 6.0 Hz, 2H), 2.70 (t, *J* = 6.0 Hz, 2H), 2.46 (s, 3H);^{13}C NMR (75 MHz, $CDCl_3$): δ 134.6, 133.8, 128.6, 126.4, 126.1, 125.6, 57.9, 52.9, 46.1, 29.2.

2-methyl-3,4-dihydroisoquinolin-2-ium iodide (19). To 2-methyl-1,2,3,4-tetrahydroisoquinoline **18** (1.47g, 10 mmol) in absolute ethanol (10 mL), KOAc (11 mmol, 1.07g) was added and the resulting mixture was heated to reflux. To the reaction mixture, a solution of I_2 (10 mmol, 2.54 g) in ethanol (10 mL) was added dropwise for 5 min. The mixture was refluxed for 1.5 h. After cooling to room temperature, the solvent was concentrated under vacuum. The residue was treated with a mixture of 6:1 acetone/ethanol (10 mL) and warmed to homogenize the solution. On cooling, KI was filtered off. The filtrate was concentrated under vacuum and recrystallized (8:1 acetone/ethanol) to afford **19** (2.18 g, 80%) as yellow solid. Mp: 127 °C; ^{1}H NMR (300 MHz, $CDCl_3$): *δ* 9.92 (s, 1H), 8.0 (t, *J* = 7.5 Hz, 1H), 7.66 (t, *J* = 9.0 Hz, 1H), 7.41 (t, *J* = 7.5 Hz, 1H), 7.35 (d, *J* = 7.5 Hz, 1H), 4.08 (t, *J* = 8.1 Hz, 2H), 3.98 (s, 3H), 3.36 (t, *J* = 8.1 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): *δ* 166.4, 138.0, 135.7, 134.1, 128.5, 128.3, 124.4, 51.0, 48.7, 25.4; MS (ESI) *m/z* $[M]^+$ calcd for $C_{10}H_{13}NO$ 146.10, found 146.11.

2-methyl-1,2,3,4-tetrahydroisoquinolin-1-ol (20). 2-Methyl-3,4-dihydroisoquinolin-2-ium iodide **19** (2.73g, 10 mmol) was dissolved in water (5 ml). The insoluble impurity was then filtered off. A brown precipitate was formed when the cooled filtrate (ice bath) was treated dropwise with 20% NaOH (5-10 mL). After an additional stirring period for 30 min, the precipitate was filtered off and dried to give **20** (1.3 g, 80%) as a brown crystalline solid. Mp: 105 °C; ^{1}H NMR (300 MHz, $CDCl_3$): *δ* 7.39 (t, *J* = 4.5 Hz, 1H), 7.19 (t, *J* = 6.0 Hz, 2H), 7.05 (t, *J* = 6.0 Hz, 1H), 4.93 (s, 1H), 3.71 (s, 1H), 3.03–2.93 (m, 1H), 2.81 (t, 2H, *J* = 6.0 Hz), 2.67–2.60 (m, 1H), 2.41 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): *δ* 137.5, 134.3, 128.2, 127.6, 127.5, 126.0, 85.7, 47.7, 40.8, 27.9; MS (ESI) *m/z* $[M-H_2O]^+$ calcd for $C_{10}H_{12}N$ 146.10, found 146.14.

2-(2-methyl-1,2,3,4-tetrahydroisoquinolin-1-yl)-1-phenylethan-1-one (21). To 2-methyl-1,2,3,4-tetrahydroisoquinolin-1-ol **20** (163 mg, 1 mmol) in methanol, acetophenone (120 mg, 1 mmol) was added and the resulting mixture was stirred for 5 h. The coupling product **21** (233 mg, 88%) was isolated as yellow liquid after short column chromatography (20% EtOAc/Hexane). ^{1}H NMR (300 MHz, $CDCl_3$): *δ* 7.97–7.95 (m, 2H), 7.56 (t, *J* = 6.6 Hz, 1H), 7.44 (t, *J* = 6.6 Hz, 2H),7.13–7.10 (m, 4H), 4.51 (t, *J* = 6.0 Hz, 1H), 3.64–3.56 (m, 1H), 3.19–3.10 (m, 2H), 3.02–2.92 (m, 1H), 2.84–2.67 (m, 2H), 2.45 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 198.8, 138.4, 137.3, 134.1, 133.0, 128.9, 128.6, 128.2, 127.4, 126.2, 126.1, 58.8, 46.9, 45.1, 42.6, 25.6; MS (ESI) *m/z* $[M+H]^+$ calcd for $C_{18}H_{20}NO$ 266.15, found 266.11.

4-methoxy-6-methyl-5-(phenylethynyl)-5,6,7,8-tetrahydro-[1,3]dioxolo[4,5-g]isoquinoline (22). To a 5 mL round bottom flask equipped with a magnetic stir bar was charged with cotarnine **1** (237 mg, 1 mmol) and phenyl acetylene (102 mg, 1 mmol) in methanol (1 mL), and the resulting mixture was stirred at room temperature for 72h. The reaction mixture was subjected to chromatography with short pad of silica gel using hexane and ethyl acetate as eluent. The product was collected to afford **22** (263 mg, 82%) as colorless liquid. ^{1}H NMR (300 MHz, $CDCl_3$): *δ* 7.40–7.39 (m, 2H), 7.25–7.20 (m, 2H), 6.34 (s, 1H), 4.94 (s, 1H), 5.88 (s, 2H), 4.04 (s, 3H), 3.29–3.02 (m, 2H), 2.80–2.67 (m, 1H), 2.67–2.62 (m, 1H), 2.59 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): *δ* 148.4, 139.9, 134.6, 131.7, 128.1, 127.9, 127.4, 123.4, 121.1, 103.0, 100.8, 85.7, 85.7, 59.6, 51.2, 46.8, 43.1, 28.8; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{20}H_{20}NO_3$ 322.1438, found 322.1437.

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FULL PAPER **KEY TOPIC:** ***C(SP^3)-H Bond Activation***

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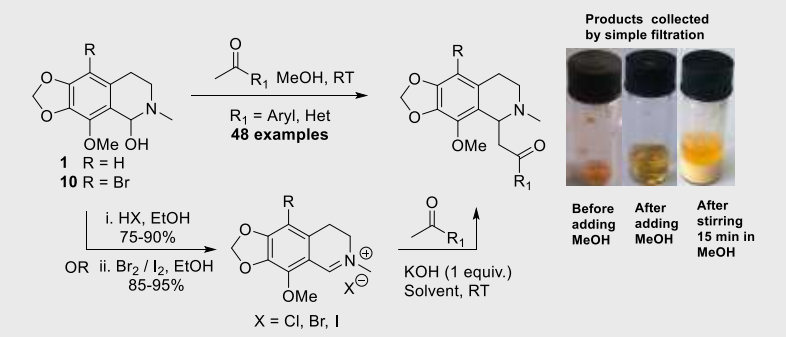
Title: **Metal Free Activation of C(SP3 H Bond, Practical and Rapid Synthesis Privileged 1-Substituted-1,2,3,4-Tetr hydro isoquinolines**



Metal Free C(SP3)-H Bond Activation: Practical, Efficient and one-pot procedure for synthesis of privileged 1,2,3,4-tetrahydroisoquinolines in multigram scale takes place under base-free conditions at room temperature, and tolerates a wide range of functionalities The reaction is highly chemo-selective, scalable in multi-gram scale, and pure products were isolated by simple filtration without work-up. Interestingly, the complementary two-step procedure from cotarnine halide salts gives the Mannich products in good yields.