Microwave-accelerated Conjugate Addition of 2-Arylindoles to Substituted β-Nitrostyrenes in the Presence of Ammonium Trifluoroacetate: An Efficient Approach for the Synthesis of a Novel Class of CB1 Cannabinoid Receptor Allosteric Modulators

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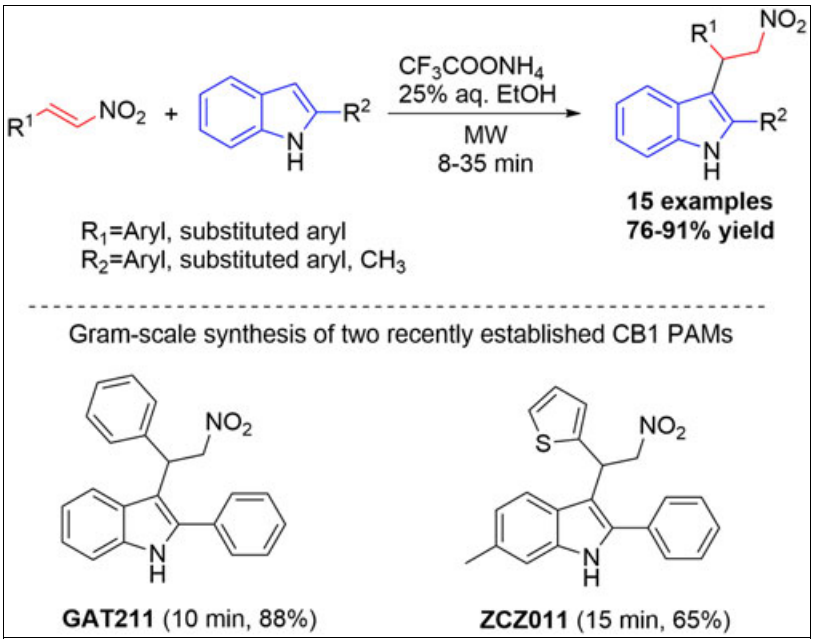


2-Arylindoles, in general, exhibit reduced reactivity towards the conjugate addition to substituted nitrostyrenes, when compared with indoles. We report here an efficient, expeditious, and high-yielding conjugate addition of 2-arylindoles to substituted β-nitrostyrenes in the presence of ammonium trifluoroacetate under microwave irradiation. This method is mild with high and reproducible yields and is selective for addition of β-nitrostyrenes when compared with other electrophiles. The results obtained from the optimized microwave method consistently provided improved yields in a shorter time compared with those of the conventional heating synthetic route.

The cannabinoid 1 receptor (CB1R), a tractable target for treating several pathologies affecting humans, is the most abundant class-A G-protein coupled receptor in the brain and is also expressed in many peripheral tissues [1]. CB1R-mediated signaling plays a vital role in many important physiological functions including learning, memory, cognition, nociception, cardiovascular function, reproduction, and neuronal development, and dysregulated CB1R activity has been implicated in the pathogenesis of disease states related to these and other physiological processes [1,2]. Although, several CB1R targeting clinical candidates have demonstrated their therapeutic utility, the undesirable on-target side effects associated with such orthosteric agonists/antagonists have greatly limited their translational potential [1,2]. Recent discovery of CB1R allosteric modulators has renewed interest in CB1R by offering a potentially safer therapeutic avenue [3]. Exemplars of small-molecule positive (PAMs) and negative (NAMs) allosteric modulators are shown in Figure 1 [3,4]. CB1 PAMs such as ZCZ011[4] and GAT211 (**1**) [5] hold promise of greater and safer clinical utility than typical CB1R orthosteric agonists because of the lack of intrinsic activity of allosteric modulators in the absence of an orthosteric ligand.

Such compounds can be synthesized in one step by Michael addition of 2-phenylindoles with suitable β-nitrostyrenes. Although such conjugate addition of

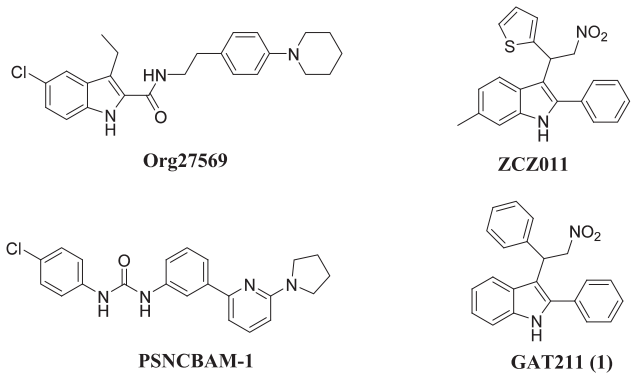


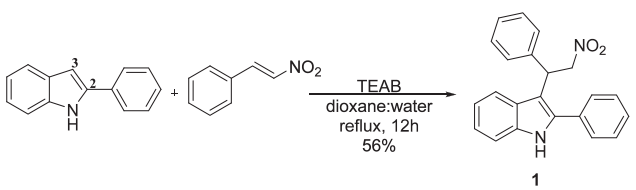
Figure 1. Some representative CB1 PAM/NAMs.

unsubstituted indoles to β-nitrostyrenes or other electrophiles at C-3 position has been studied in depth, and a variety of methods have been reported [6], relatively few conditions are available for extending such additions to 2-phenylindoles in which the C-3 position is less reactive and sterically hindered because of phenyl substitution at C-2 position [7]. The reactivity mismatch between the highly electrophilic/reactive β-nitrostyrene and the sterically hindered/less reactive and relatively electron deficient 2-phenylindoles often leads to longer reaction times with poor yields. The acid-catalyzed conjugate addition of such 2-phenylindoles to β-nitrostyrene requires careful control of acidity to prevent side reactions such as dimerization or polymerization of indoles [8]. Thus, identification of an efficient catalyst and development of better reactions conditions are required for such an addition reaction.

Previously, we reported the synthesis of **1** by using tetraethylammonium bromide (TEAB) (Scheme 1). However, this method was relatively inefficient in terms of time (12 h) and yield (56%). The need for rapid lead optimization and scale up in gram quantities for profiling the therapeutic utility of such modulators demanded our focus towards the development of a more facile, high-yield method for synthesis of **1** and its analogs.

Microwave (MW) irradiation accelerates the rates and yields of many chemical reactions, including conjugate addition reactions [9]. Our laboratory is actively involved in utilizing microwave-accelerated methodologies for facilitating expeditious library synthesis of biological

Scheme 1. Synthesis of **1** using our previously reported protocol.[5]



active compounds [10]. In this regard, we attempted MW irradiation for the reaction (Scheme 1) but unfortunately did not obtain much improvement. Babu *et al.* reported the synthesis of **1** by using tetrabutylammonium bromide (TBAB) under reflux conditions in acetonitrile in quantitative yields [7]. However, in our hands, even after repeated attempts, this reaction did not provide yields greater than 62%, and longer reaction times were required. MW irradiation of this reaction yielded only minor improvement, prompting us to search for alternative conditions. Conjugate addition of β-nitrostyrenes with indole and 2-methylindole has been reported in superheated water at 150°C without any catalyst [11]. Our attempt to extend the scope of this method to 2-phenylindole, however, gave **1** in moderate yields (~55%) with longer reaction time, presumably because of solubility issues and thermal degradation of starting materials in water. Several Lewis acids reported for Michael addition of indoles on β-nitrostyrenes, zinc triflate is a well-studied and high-yielding catalyst [12]. However, this catalyst has not been explored for Michael addition of 2-phenylindole as a substrate. We followed the reported protocol by carrying out above reaction at room temperature in presence of zinc trifluoromethanesulfonate (20 mol%). Although satisfactory yield (65%) was obtained, longer reaction time (>24 h) prompted us to investigate further this reaction under microwave conditions.

We attempted the optimization of the MW version of this reaction using an array of solvents at 100°C (Table 1), and we found EtOH to be the best solvent (entry 11, Table 1). We further performed this reaction in EtOH at various temperatures (50, 75, 125, and 150°C), but no significant enhancement in yield was obtained.

To improve the yields, we also explored metal-free conditions, which not only add commercial value but also make the reaction environment friendly [13]. We used

Table 1

Optimization of reaction conditions for Michael addition of 2-phenylindole to β-nitrostyrene in presence of zinc trifluoromethanesulfonate.[a]

Entry	Solvent	Time (min)	Yield (%)
1	Toluene	15	60
2	$CHCl_3$	15	53
3	Ether	15	63
4	THF	15	59
5	DME	12	64
6	DMF	15	45
7	DMA	15	40
8	DMSO	15	38
9	CH_3CN	15	51
10	H_2O	15	50
11	EtOH	10	68

[a]MW irradiation at 100°C; 20 mol% $(CF_3SO_3)_2Zn$.

several quaternary ammonium salts, which are biodegradable [14], provide milder reaction conditions, and are water as well as ethanol soluble at ambient temperatures (Table 2). The best yield (80%) was obtained with CF_3COONH_4 as a catalyst using absolute ethanol as a solvent (entry 4, Table 2). CF_3COONH_4 is a least explored catalyst [15], and this is the first report of its application to such Michael addition reaction.

Table 2

Effect of different ammonium salts on reaction time and yield.[a]

Entry	Catalyst	Time (min)	Yield (%)
1	TBAB	15	42
2	$CF_3SO_3NH_4$	10	69
3	CH_3COONH_4	20	71
4	CF_3COONH_4	10	80
5	$HCOONH_4$	10	64

[a]MW, 100°C, EtOH; 20 mol% catalyst.

Table 3

Effect of different percentage of aq. ethanol on reaction yield.[a]

Entry	mol% of CF_3COONH_4	% of aq. EtOH	Yield (%)
1	20	100	80
2	20	50	87
3	20	25	88
4	10	25	81
5	50	25	89

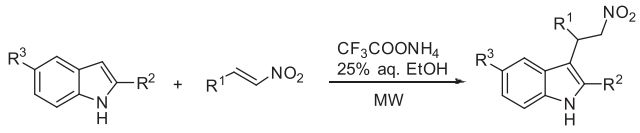
[a]MW, 100°C, EtOH, 10 min.

As the presence of water was found to favor the reaction yield, we attempted use of different percentages of aqueous ethanol as a solvent with ammonium trifluroacetate at 100°C (Table 3). The best yields were obtained with 25% and 50% aqueous ethanol. We also altered the amount of CF_3COONH_4 (Table 3), and 20 mol% was found to be optimum. Reactions performed in aqueous ethanol when cooled to room temperature led to product precipitation in acceptable purity, which was an advantage especially for reactions carried out on gram scale.

We applied these optimized conditions (25% aq EtOH, 100°C, and CF_3COONH_4) for the conjugate addition of different 2-arylindoles on various nitroalkenes (Table 4). β-nitrostyrenes bearing electron withdrawing groups (entries 5, 7, and 8) required lesser time as compared with electron-donating substrates (entries. 2, 3, 4, and 11). A significant increase in reaction time was necessitated when a strong electron withdrawing group like nitro group was present at 5-position of indole (entry 14, Table 4), which led to that the decreased nucleophilicity at C3 position of indole. Heterocyclic and polycyclic β-nitrostyrenes also provided corresponding Michael adduct in good yields (entry 9–11, Table 4). To

Table 4

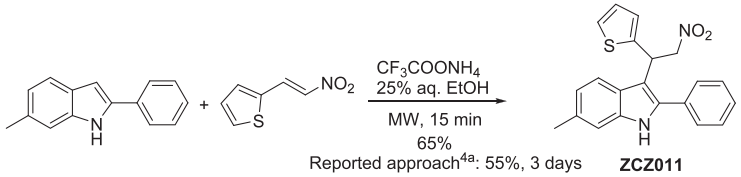
Michael addition of 2-arylindole to different β-nitrostyrenes on 6.50 mmol scale.



				Microwave		Conventional heating	
Compound	R^1	R^2	R^3	Time (min)	Isolated yield (%)[b]	Time (h)	Isolated yield (%)[b]
1	Ph	Ph	H	10	88	3.5	78
2	2-CH_3OPh	Ph	H	20	87	6	76
3	4-CH_3OPh	Ph	H	20	86	6	74
4	3-CH_3OPh	Ph	H	18	81	8	70
5	2CF_3-Ph	Ph	H	10	84	4	72
6	2,6-diClPh	Ph	H	25	81	14	77
7	4-CNPh	Ph	H	9	85	4	74
8	2-NO_2Ph	Ph	H	8	80	3	70
9	2-furyl	Ph	H	22	89	12	76
10	2-Naphthyl	Ph	H	15	76	12	71
11	4-(piperdinyl)Ph	Ph	H	35	77	24	62
12	Ph	2-Naphthyl	H	15	78	6	69
13	Ph	CH_3	H	10	91	6	83
14	Ph	Ph	5-NO_2	65	89	20	38
15	Ph	4-Cl Ph	H	20	79	6	69

[a]on 6.50 mmol scale;
[b]Isolated yield

Scheme 2. Gram scale synthesis of CB1PAM ZCZ011.



expand further the scope of this method, we utilized napthyl and substituted phenyl ring well as methyl group at C-2 of the indole. We observed bulky and electron withdrawing groups took longer reaction time (entry 12) whereas an electron-donating group such as methyl favored the Michael addition acceleration in higher yield (entry 13) with shorter reaction time.

To demonstrate further the selectivity of our method towards different reactive Michael acceptors, we performed the aforementioned reaction in the presence of methylacrylate, ethyl cinnamate, acrylonitrile, and nitrostyrene. Interestingly, the only Michael adduct of β-nitrostyrene **4** was obtained, indicating the selectivity of the reaction. To test the relative efficiency of microwave acceleration, we also attempted a conventional heating protocol. Microwave acceleration clearly demonstrated higher yields in all examples (Table 4).

We then elaborated the utility of this method by successful application to the rapid synthesis of compound ZCZ011, which was produced in 65% yield in 15 min (Scheme 2) under microwave irradiation as compared with the literature reported yield [4] and time (3 days). Using this optimized method, we made a library of analogs of **4** as potential CB1 PAMs, synthesis and biochemical characterization of which will be published elsewhere.

In conclusion, we have developed an efficient, mild, microwave-accelerated, and high-yielding method for addition of varieties of 2-arylindoles to β-nitrostyrenes. This approach is valuable and useful for rapid synthesis of biologically significant compounds.

GENERAL REMARKS

Microwave reactions were conducted using a Biotage® Initiator Classic microwave synthesizer (Biotage, Charlotte, NC). Reactions were performed in glass vessels (capacity, 5 to 20 mL) equipped with magnetic stirring bar and sealed with a septum. The target temperature was set and maintained constant during the reaction.

GENERAL PROCEDURE

In a 20-mL microwave vial 2-arylindole derivative (1.0 eq.; 6.5 mmol), nitro alkene (1.3 eq.; 8.45 mmol), of CF_3COONH_4 (0.2 eq.; 1.3 mmol) were taken in of 25% aq. EtOH (12 mL). The tube was sealed and introduced in the microwave reactor. The tube was irradiated for an appropriate time at 100°C under stirring. After completion of reaction, the reaction mixture was diluted with cold water followed by extraction with dichloromethane (three times). Combined dichloromethane layer was evaporated under vacuum, the residue was purified by flash chromatography using Biotage SP1 instrument using normal phase GRACE™ columns (40 μm particle size) to acquire pure product.

3-(2-Nitro-1-phenylethyl)-2-phenyl-1*H*-indole (1; GAT211). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.13 (br s, 1H, NH), 7.51 (d, *J* = 8.0 Hz, 1H), 7.46–7.39 (m, 5H), 7.36 (br d, *J* = 8.0 Hz, 1H), 7.34–7.31 (m, 2H), 7.31–7.26 (m, 2H), 7.25–7.18 (m, 2H, esp. 7.20, ddd, *J* = 8.0 Hz, *J* = 7.0 Hz, *J* = 1.0 Hz, 1H), 7.10 (ddd, *J* = 8.0 Hz, *J* = 7.0 Hz, *J* = 1.0 Hz, 1H), 5.31 (dd as t, *J* = 8.0 Hz, 1H), 5.17 (dd, *J* = 12.5, 7.5 Hz, 1H), 5.12 (dd, *J* = 12.5, 7.5 Hz, 1H); MS (ESI) (*m/z*): 343 $[M + H]^+$. HRMS *m/z* calculated for $C_{22}H_{18}N_2O_2$ $[M]^+$ 342.1368, found 342.1364.

3-(1-(2-Methoxyphenyl)-2-nitroethyl)-2-phenyl-1*H*-indole (2). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.14 (br s, 1H, NH), 7.64 (dd, *J* = 8.0 Hz, 0.5 Hz, 1H), 7.45–7.36 (m, 6H), 7.35 (dd, *J* = 7.5 Hz, 1.5 Hz, 1H), 7.28–7.18 (m, 2H, esp. 7.21, ddd, *J* = 8.5 Hz, 7.5 Hz, 1.5 Hz, 1H), 7.13 (ddd, *J* = 8.5 Hz, 7.5 Hz, 1.5 Hz, 1H), 6.89 (dd, *J* = 8.0 Hz, 1.0 Hz, 1H), 6.84 (td, *J* = 7.5 Hz, 1.0 Hz, 1H), 5.60 (dd, *J* = 9.0 Hz, 6.5 Hz, 1H), 5.17 (dd, *J* = 12.5 Hz, 6.5 Hz, 1H), 5.14 (dd, *J* = 12.5 Hz, 9.0 Hz, 1H), 3.77 (s, 3H). MS (ESI) (*m/z*): 373 $[M + H]^+$. HRMS *m/z* calculated for $C_{23}H_{20}N_2O_3$ $[M]^+$ 372.1474, found 342.1471.

3-(1-(4-Methoxyphenyl)-2-nitroethyl)-2-phenyl-1*H*-indole (3). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.13 (br s, 1H, NH), 7.53 (br d, *J* = 8.0 Hz, 1H), 7.48–7.39 (m, 5H), 7.38 (br d, *J* = 8.5 Hz, 1H), 7.27–7.23 (m, 2H), 7.21 (ddd, *J* = 8.0 Hz, 7.0 Hz, 1.0 Hz, 1H), 7.11 (ddd, *J* = 8.0 Hz, 7.0 Hz, 1.0 Hz, 1H), 6.82 (d, *J* = 9.0 Hz, 2H), 5.26 (dd as br t, *J* = 8.0 Hz, 1H), 5.14 (dd, *J* = 12.0 Hz, 7.0 Hz, 1H), 5.09 (dd, *J* = 12.5 Hz, 8.5 Hz, 1H), 3.76 (s, 3H); MS (ESI) (*m/z*): 373 $[M + H]^+$. HRMS *m/z* calculated for $C_{23}H_{20}N_2O_3$ $[M]^+$ 372.1474, found 342.1480.

3-(1-(3-Methoxyphenyl)-2-nitroethyl)-2-phenyl-1*H*-indole (4). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.16 (br s, 1H, NH), 7.54 (dd, *J* = 8.0 Hz, 0.5 Hz, 1H), 7.47–7.39 (m, 5H), 7.36 (br d, *J* = 8.0 Hz, 1H), 7.25–7.17 (m, 2H), 7.11 (ddd,

J = 8.5 Hz, 7.5 Hz, 1.0 Hz, 1H), 6.93 (br d, *J* = 8.0 Hz, 1H), 6.88 (t, *J* = 2.0 Hz, 1H), 6.77 (dd, *J* = 8.5 Hz, 2.5 Hz, 1H), 5.28 (dd as br t, *J* = 8.0 Hz, 1H), 5.16 (dd, *J* = 12.5 Hz, 7.0 Hz, 1H), 5.12 (dd, *J* = 12.5 Hz, 8.5 Hz, 1H), 3.71 (s, 3H). MS (ESI) (*m/z*): 373 $[M + H]^+$. HRMS *m/z* calculated for $C_{23}H_{20}N_2O_3$ $[M]^+$ 372.1474, found 342.1477.

3-(2-Nitro-1-(2-(trifluoromethyl)phenyl)ethyl)-2-phenyl-1*H*-indole (5). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.16 (br s, 1H, NH), 7.83 (br d, *J* = 8.0 Hz, 1H), 7.76 (dd, *J* = 8.0 Hz, 1.0 Hz, 1H), 7.68 (dd, *J* = 7.5 Hz, 1.0 Hz, 1H), 7.44–7.39 (m, 5H), 7.38–7.33 (m, 3H), 7.27–7.23 (m, 1H), 7.21 (ddd, *J* = 8.5 Hz, 7.5 Hz, 1.5 Hz, 1H), 5.76 (dd, *J* = 10.5 Hz, 5.5 Hz, 1H), 5.34 (dd, *J* = 13.5 Hz, 10.5 Hz, 1H), 4.89 (dd, *J* = 13.5, 5.5 Hz, 1H); MS (ESI) (*m/z*): 410.12 $[M + H]^+$. MS (ESI) (*m/z*): 411 $[M + H]^+$. HRMS *m/z* calculated for $C_{23}H_{17}F_3N_2O_2$ $[M]^+$ 410.1242, found 410.1248.

3-(1-(2,6-Dichlorophenyl)-2-nitroethyl)-2-phenyl-1*H*-indole (6). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.02 (br s, 1H, NH), 7.41–7.27 (m, 7H), 7.19 (d, *J* = 8.0 Hz, 2H), 7.17 (dd, *J* = 8.0 Hz, 1.0 Hz, 1H), 7.08–7.03 (m, 2H), 6.20 (dd, *J* = 8.5 Hz, 7.0 Hz, 1H), 5.27 (dd, *J* = 13.5 Hz, 6.5 Hz, 1H), 5.24 (dd, *J* = 13.0 Hz, 9.0 Hz, 1H); MS (ESI) (*m/z*): 411 $[M + H]^+$. HRMS *m/z* calculated for $C_{22}H_{16}Cl_2N_2O_2$ $[M]^+$ 410.0589, found 410.0585.

4-(2-Nitro-1-(2-phenyl-1*H*-indol-3-yl)ethyl)benzonitrile (7). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.22 (br s, 1H, NH), 7.58 (d, *J* = 8.5 Hz, 2H), 7.52–7.46 (m, 3H), 7.46–7.39 (m, 6H), 7.25 (ddd, *J* = 8.0 Hz, 7.0 Hz, 1.0 Hz, 1H), 7.14 (ddd, *J* = 8.0 Hz, 7.0 Hz, 1.0 Hz, 1H), 5.36 (dd as br t, *J* = 8.0 Hz, 1H), 5.23 (dd, *J* = 12.5 Hz, 8.0 Hz, 1H), 5.11 (dd, *J* = 12.5 Hz, 7.5 Hz, 1H); MS (ESI) (*m/z*): 368 $[M + H]^+$. HRMS *m/z* calculated for $C_{23}H_{17}N_3O_2$ $[M]^+$ 367.1321, found 367.1323.

3-(2-Nitro-1-(2-nitrophenyl)ethyl)-2-phenyl-1*H*-indole (8). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.18 (br s, 1H, NH), 7.84 (dd, *J* = 8.0 Hz, 1.5 Hz, 1H), 7.77 (dd, *J* = 8.0 Hz, 1.0 Hz, 1H), 7.64 (dd, *J* = 8.0 Hz, 0.5 Hz, 1H), 7.49 (td, *J* = 7.5 Hz, 1.5 Hz, 2H), 7.45–7.37 (m, 5H), 7.33–7.28 (m, 2H), 7.27–7.22 (m, 1H), 7.18 (ddd, *J* = 8.0 Hz, 7.0 Hz, 1.0 Hz, 1H), 5.93 (dd, *J* = 9.0 Hz, 7.0 Hz, 1H), 5.30 (dd, *J* = 13.5 Hz, 9.0 Hz, 1H), 5.16 (dd, *J* = 13.5 Hz, 7.0 Hz, 1H); MS (ESI) (*m/z*): 388 $[M + H]^+$. HRMS *m/z* calculated for $C_{22}H_{17}N_3O_4$ $[M + H]^+$ 388.1219, found 388.1223.

3-(1-(Furan-2-yl)-2-nitroethyl)-2-phenyl-1*H*-indole (9). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.17 (br s, 1H, NH), 7.56 (dd, *J* = 8.0 Hz, 0.5 Hz, 1H), 7.54–7.47 (m, 4H), 7.47–7.42 (m, 1H), 7.39 (br d, *J* = 8.0 Hz, 1H), 7.37 (d, *J* = 2.0 Hz, 1H), 7.22 (ddd, *J* = 8.5 Hz, 7.5 Hz, 1.5 Hz, 1H), 7.12 (ddd, *J* = 8.0 Hz, 7.0 Hz, 1.0 Hz, 1H), 6.30 (dd, *J* = 3.5 Hz, 2.0 Hz, 1H), 6.14 (dt, *J* = 3.5 Hz, 1.0 Hz, 1H), 5.36 (td, *J* = 7.5 Hz, 0.5 Hz, 1H), 5.24 (dd, *J* = 12.5 Hz, 7.5 Hz, 1H), 4.92 (dd, *J* = 12.5 Hz, 7.5 Hz, 1H); MS (ESI) (*m/z*): 333 $[M + H]^+$. HRMS *m/z* calculated for $C_{20}H_{16}N_2O_3$ $[M]^+$ 332.1161, found 332.1168.

3-(1-(Naphthalen-2-yl)-2-nitroethyl)-2-phenyl-1*H*-indole (10). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.19 (br s, 1H, NH), 7.82–7.73 (m, 4H), 7.55 (dd, *J* = 8.0 Hz, 0.5 Hz, 1H), 7.50–7.40 (m, 9H), 7.23 (ddd, *J* = 8.0 Hz, 7.0 Hz, 1.0 Hz, 1H), 7.10 (ddd, *J* = 8.0 Hz, 7.0 Hz, 1.0 Hz, 1H), 5.48 (dd as t, *J* = 7.0 Hz, 1H), 5.32 (dd, *J* = 12.5 Hz, 7.0 Hz, 1H), 5.22 (dd, *J* = 12.5 Hz, 8.5 Hz, 1H); MS (ESI) (*m/z*): 393 $[M + H]^+$. HRMS *m/z* calculated for $C_{26}H_{20}N_2O_2$ $[M]^+$ 392.1525, found 392.1530.

3-(2-Nitro-1-(4-(piperidin-1-yl)phenyl)ethyl)-2-phenyl-1*H*-indole (11). ^{1}H NMR (DMSO-d_6, 500 MHz) δ 11.41 (br s, 1H, NH), 7.64 (d, *J* = 8.0 Hz, 1H), 7.59–7.41 (m, 5H), 7.37 (d, *J* = 8.0 Hz, 1H), 7.18–7.04 (m, 3H), 6.98 (t, *J* = 7.5 Hz, 1H), 6.83 (d, *J* = 8.5 Hz, 2H), 5.52–5.27 (m, 2H), 5.09 (dd as t, *J* = 8.5, 1H), 3.17–2.95 (m, 4H), 1.67–1.36 (m, 6H); MS (ESI) (*m/z*): 426 $[M + H]^+$. HRMS *m/z* calculated for $C_{27}H_{27}N_3O_2$ $[M + H]^+$ 426.2103, found 426.2120.

2-(Naphthalen-2-yl)-3-(2-nitro-1-phenylethyl)-1*H*–indole (12). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.27 (br s, 1H, NH), 7.94 (d, *J* = 8.5 Hz, 1H), 7.91–7.87 (m, 2H), 7.86–7.81 (m, 1H), 7.61–7.51 (m, 4H), 7.44 (d, *J* = 8.0 Hz, 1H), 7.40–7.35 (m, 2H), 7.35–7.29 (m, 2H), 7.28–7.22 (m, 2H), 7.15 (ddd, *J* = 8.0 Hz, 7.0 Hz, 1.0 Hz, 1H), 5.41 (dd as t, *J* = 8.0 Hz, 1H), 5.21 (dd, *J* = 12.5 Hz, 7.5 Hz, 1H), 5.18 (dd, *J* = 12.5 Hz, 8.5 Hz, 1H); MS (ESI) (*m/z*): 393 $[M + H]^+$. HRMS *m/z* calculated for $C_{26}H_{20}N_2O_2$ $[M]^+$ 392.1525, found 392.1530.

2-Methyl-3-(2-nitro-1-phenylethyl)-1*H*–indole (13). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.85 (br s, 1H, NH), 7.36 (dd, *J* = 8.0 Hz, 0.5 Hz, 1H), 7.34–7.25 (m, 5H), 7.24–7.20 (m, 1H), 7.11 (ddd, *J* = 8.5 Hz, 7.5 Hz, 1.0 Hz, 1H), 7.02 (ddd, *J* = 8.0 Hz, 7.0 Hz, 1.0 Hz, 1H), 5.26–5.16 (m, 2H), 5.11 (dd, *J* = 10.5 Hz, 7.5 Hz, 1H), 2.40 (s, 3H); MS (ESI) (*m/z*): 281 $[M + H]^+$. HRMS *m/z* calculated for $C_{17}H_{16}N_2O_2$ $[M]^+$ 280.1212, found 280.1220.

5-Nitro-3-(2-nitro-1-phenylethyl)-2-phenyl-1*H*-indole (14). ^{1}H NMR (DMSO-d_6, 500 MHz) δ 12.27 (br s, 1H, NH), 8.46 (d, *J* = 2.0 Hz, 1H), 8.03 (dd, *J* = 9.0 Hz, 2.0 Hz, 1H), 7.63–7.49 (m, 6H), 7.37–7.30 (m, 4H), 7.27–7.22 (m, 1H), 5.64 (dd, *J* = 13.5 Hz, 7.5 Hz, 1H), 5.44 (dd, *J* = 13.0 Hz, 9.0 Hz, 1H), 5.27 (dd as t, *J* = 8.0 Hz, 1H); MS (ESI) (*m/z*): 388 $[M + H]^+$. HRMS *m/z* calculated for $C_{22}H_{17}N_3O_4$ $[M + H]^+$ 388.1219, found 388.1300.

2-(4-Chlorophenyl)-3-(2-nitro-1-phenylethyl)-1*H*–indole (15). ^{1}H NMR (DMSO-d_6, 500 MHz): δ 11.50 (br s, 1H, NH), 7.68–7.59 (m, 3H, esp. 7.63 (d, *J* = 8.5 Hz, 2H), 7.54 (d, *J* = 8.0 Hz, 2H), 7.38 (d, *J* = 8.0 Hz, 1H), 7.34–7.27 (m, 4H), 7.21 (tt, *J* = 7.0 Hz, 1.5 Hz, 1H), 7.12 (br t, *J* = 8.0 Hz, 1H), 6.98 (br t, *J* = 8.0 Hz, 1H), 5.56 (dd, *J* = 13.5 Hz, 7.5 Hz,1H), 5.44 (dd, *J* = 13.5 Hz, 9.5 Hz, 1H), 5.17 (dd as br t, *J* = 8.0 Hz, 1H); MS (ESI) (*m/z*): 377 $[M + H]^+$. HRMS *m/z* calculated for $C_{22}H_{17}ClN_2O_2$ $[M]^+$ 376.0979, found 376.0959.

6-Methyl-3-(2-nitro-1-(thiophen-2-yl)ethyl)-2-phenyl-1*H*-indole (ZCZ011).. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.04 (br s,1H, NH), 7.52–7.45 (m, 4H), 7.45–7.38 (m, 2H), 7.21–7.18 (m, 2H), 6.96 (dd, J = 8.0 Hz, 1.5 Hz, 1H), 6.95–6.91 (m, 2H), 5.47 (t, J = 8.0 Hz, 1H), 5.19 (dd, J = 12.5 Hz, 7.0 Hz, 1H), 5.07 (dd, J = 12.5 Hz, 8.0 Hz, 1H), 2.46 (s, 3H); MS (ESI) (m/z): 363 $[M + H]^+$. HRMS m/z calculated for $C_{21}H_{18}N_2O_2S$ $[M]^+$ 362.1089, found 362.1090.

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