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Microwave-assisted synthesis of (2-butyl-5-nitrobenzo[*b*]furan-3-yl)-[4-(substituted ethynyl)phenyl]methanones

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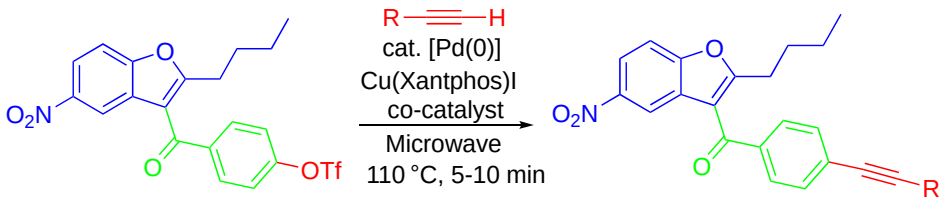
Abstract

We report a new method for the efficient and rapid synthesis of (2-butyl-5-nitrobenzo[*b*]furan-3-yl)[4-(substituted ethynyl)phenyl]methanones using a Pd-Cu catalyzed microwave-assisted Sonogashira coupling reaction. In comparison to the conventional heating procedure, the time of synthesis and effort are significantly reduced in the present method, without side-product formation. Microwave irradiation considerably accelerated the formation of (2-butyl-5-nitrobenzo[*b*]furan-3-yl)[4-(substituted ethynyl)phenyl]methanone analogues.



Keywords: Benzo[*b*]furan, Sonogashira approach, microwave-assisted synthesis

Introduction

Oxygen containing heterocycles form one of the largest group of compounds in organic chemistry. Among them, one of the most important are benzo[*b*]furans, a class of fused-ring heterocyclic compounds. Several derivatives of benzo[*b*]furan have been recognized as biologically and pharmacologically relevant molecules.[1] Benzo[*b*]furan derivatives exhibit significant activity against various therapeutic areas including antifungal,[2] antitubercular,[3] antiinflammatory,[4] anticonvulsant,[5] anticancer,[6] anti-HIV,[7] analgesic,[8] antiparasitic,[9] antihyperlipidemic,[10] antioxidant,[11] antidiabetic,[12] antihypertensive,[13] hypotensive,[14] arrhythmic activities,[15] and so on. Additionally, such heterocyclic compounds are found in various branches of chemical research, such as in polymer,[16] dyes industries,[17] and in silver photography.[18] Benzo[*b*]furan derivatives are important heterocycles which are frequently found as both bioactive compounds and organic materials. The benzo[*b*]furan moiety is found in structurally simple drugs like Ramelteon[19] **I**, Amiodarone[20] **II**, Vilazodone[21] **III**, Dronedarone[22] **IV**, Pyridylbenzofuran[23] **V**, Methoxsalen[24] **VI** (Figure 1). Although microwave assisted and numerous synthetic approaches have been developed to prepare this family of compounds during the past decades, general protocols for the synthesis of these compounds are still of high interest.[25-27]

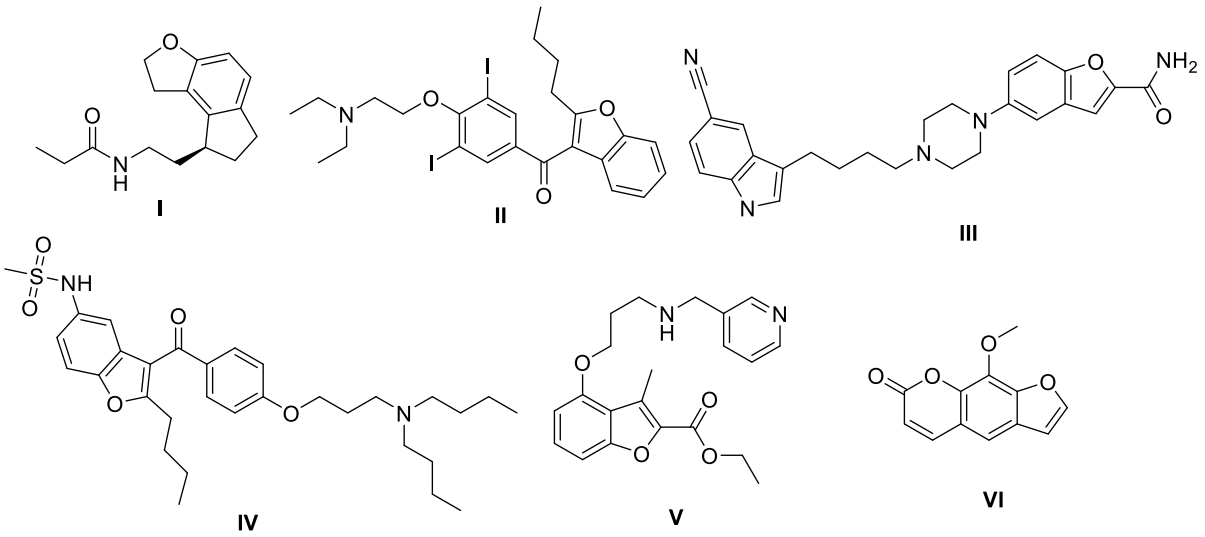


Figure 1 Representative examples of some drugs containing the benzo[*b*]furan moiety.

The palladium catalyzed coupling of terminal acetylenes with aryl triflates (the Sonogashira cross-coupling reaction) is an effective and widely-used method to form new carbon-carbon bonds.[28,29] At present, the Sonogashira reaction has been widely used to couple a terminal *sp*-hybridized carbon of an alkyne with an sp^2 carbon of an aryl or vinyl halide (or triflate),[30,31] It also plays a key role in the synthesis of many natural products,[32] pesticides, pharmaceuticals[33] and new materials and nano-molecular devices.[34] Since the discovery of the Sonogashira reactions, the most widely used catalysts are Pd-type compounds. Many cross-coupling reactions catalyzed by Pd/Cu co-catalyst involve cross-coupling of a terminal alkyne with a halogenated or triflyloxy-benzene, however the reactions coupling of terminal alkynes with halogenated or trifloxy heterocycles have been investigated in very few numbers.

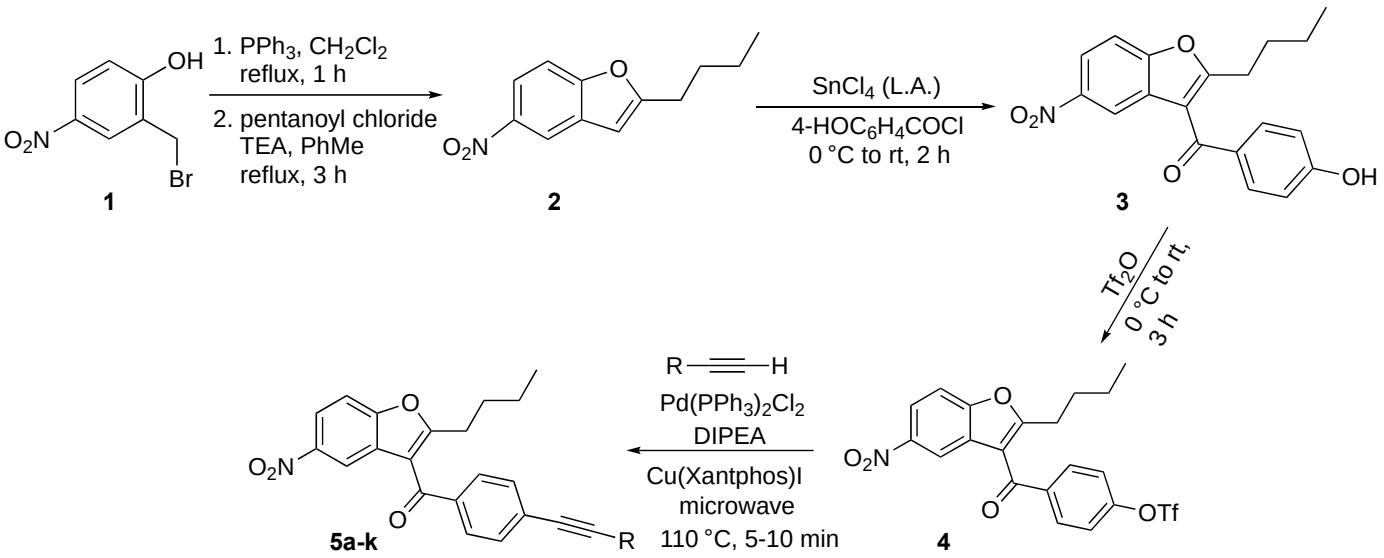
Microwave irradiation is used to promote chemical reactions, and a number of reviews have advocated the use of microwave technology in organic synthesis.[35] Microwaves provide a powerful way to carry out synthetic chemistry and the ability of microwaves to shorten reaction times, increase reaction yields and to

facilitate reactions that are otherwise unsuccessful under conventional conditions, are properties that medicinal chemists often look for to optimize their everyday procedures.[36]

Herein, we report a synthesis of novel (2-butyl-5-nitrobenzo[*b*]furan-3-yl)[4-(substituted ethynyl)phenyl]-methanones employing an environment-friendly microwave irradiation method via benzo[*b*]furan derivatives as intermediates.

Results and Discussion

The synthesis of the title compounds was carried out by both microwave irradiation and conventional heating procedures as shown in Scheme 1. 2-(Bromomethyl)-4-nitrophenol (**1**) was taken as starting material. The first step involved formation of 2-butyl-5-nitrobenzo[*b*]furan (**2**) from **1** in a two-step *in situ* synthesis, where firstly triphenylphosphine in DCM as solvent was added, followed by reflux for one hour, then triethylamine and pentanoyl chloride were added and the mixture heated at reflux in toluene for three hours to form 2-butyl-5-nitrobenzo[*b*]furan (**2**) in 95% yield.



Scheme 1

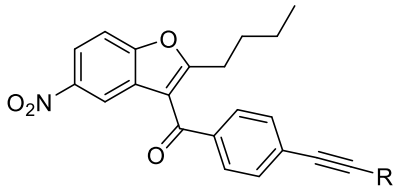
In the next step, a Friedel–Crafts acylation reaction on **2** using $SnCl_4$ as Lewis acid with 4-hydroxybenzoyl chloride in dichloromethane as a solvent at 0 °C to rt for two hours gave (2-butyl-5-nitrobenzo[*b*]furan-3-yl)(4-hydroxyphenyl)methanone (**3**) in 88% yield. Subsequent triflate formation using trifluoromethanesulfonic anhydride (Tf_2O) in dichloromethane with pyridine as a base at 0 °C to rt for three hours, provided 4-(2-butyl-5-nitrobenzo[*b*]furan-3-carbonyl)phenyl trifluoromethanesulfonate (**4**) in 88% yield. The structures of compounds **3** and **4** were confirmed by ^{1}H NMR, mass spectra and elemental analyses.

Sonogashira coupling of the triflate **4** with various substituted terminal acetylene derivatives under microwave irradiation and conventional heating, followed by simple work-up yielded (2-butyl-5-nitrobenzo[*b*]furan-3-yl)[4-(substituted ethynyl)phenyl]methanones (**5a-k).** The microwave irradiation provided excellent yields compared to conventional heating. The structures of compounds **5a-k** were characterized by various spectroscopic techniques such as FT-IR, ^{1}H NMR, ^{13}C NMR, mass spectral and elemental analyses; e.g. the IR spectrum of compounds **5a, 5b, 5c, 5d, 5e, 5h, 5j,** and **5k** showed an acetylenic

band at 2220 cm^{-1}, and C=O stretching at 1630 cm^{-1}; the ^{1}H NMR spectrum of all products showed signals in the aromatic region, between or near about 7-8 ppm and in the aliphatic region in between or near about 0-3 ppm ; the ^{13}C NMR spectrum of compound **5b, 5c, 5d, 5e, 5f, 5g, 5i,** and **5j** showed acetylenic carbons in the regions 91-98 and 75-88 ppm. LC-MS analysis of compounds **5a** and **5b** showed 100% purity. The mass spectra and C, H, N analysis results of all compounds are in agreement with the assigned structures. The reaction times and yields of compounds **5a-k** by microwave and conventional methods are given in Table 1.

The acetylenes with aliphatic substituents (entries **5f, 5g, 5h** and **5i**) were formed in slightly higher yields than those with aromatic substituents (entry- **5a, 5b, 5c, 5d, 5e** and **5j**) under microwave irradiation at 110 °C and 70-80 W for 5-10 minute in a sealed vessel, as compared with the conventional heating. Compound **5k** was formed in higher yield by both microwave and conventional methods at 80 °C, compared to all other compounds due to the use of trimethylsilylacetylene. Formation of all the desired compounds was accelerated by microwave irradiation, being obtained in 5-10 minutes with higher yields as compared with the conventional heating method.

Table 1. Synthesis of compounds **5a-k** by microwave and conventional heating



5a-k

Comp.	R	Microwave irradiation		Conventional heating	
		Time (Min)	Yield (%)	Time (Min)	Yield (%)
5a	4-tolyl	10	79	10	-
5b	2-fluorophenyl	10	83	10	3
5c	phenyl	10	88	10	4
5d	4-*n*-propylphenyl	10	81	10	3
5e	4-fluorophenyl	10	85	10	3
5f	cyclopropyl	05	91	10	6
5g	cyclopentyl	05	90	10	7
5h	cyclohexyl	05	87	10	5
5i	*n*-pentyl	05	93	10	8
5j	4-ethylphenyl	10	81	10	8
5k	H	05	94	10	10

Conclusions

In conclusion, we report a simple, efficient, rapid and environment-friendly method for the synthesis of novel (2-butyl-5-nitrobenzo[b]furan-3-yl)[4-(substituted ethynyl)phenyl]methanones employing various acetylene substrates using microwave-assisted Pd-catalysed and Cu(Xantphos)I co-catalysed Sonogashira coupling

reactions. The advantages of microwave irradiation were avoidance of the formation of side products, and also useful in the case of catalyst, to avoid the formation of palladium oxide and triphenylphosphine oxide (TPPO) complex. Furthermore, we found that the reaction is generally tolerant of all electron-withdrawing, electron-donating, aromatic and aliphatic substituents. The structures of all compounds were supported by mass and elemental analyses as well as spectral data such as FT-IR and ^{1}H NMR, and some of the compounds were characterized by ^{13}C NMR and LC-MS analysis. The straightforward synthesis of these compounds from readily available starting materials should open a new access for novel benzo[*b*]furan heterocycles with potentially interesting biological and pharmaceutical activities.

Experimental Section

General. All purchased chemicals were used without further purification. Reactions were monitored by thin layer chromatography (TLC) on silica gel-G plates (G60 F254 (Merck)) of 0.5 mm thickness, visualizing with ultraviolet light (254 and 365 nm), or with iodine vapor or aq. $KMnO_4$. Melting points were determined using a Buchi B-540 capillary apparatus. IR data were recorded on a Shimadzu FT-IR-8400 instrument using DRS (diffusive reflectance system) method and are reported in cm^{-1} (KBr). NMR spectra were recorded on a Bruker Avance 400 MHz spectrometer (400 MHz for ^{1}H NMR and 101 MHz for ^{13}C NMR) respectively in deuterated solvents like $CDCl_3$ or DMSO-d_6 and chemical shifts are referenced to the solvent residual signals with respect to tetramethylsilane; ^{1}H NMR chemical shifts are designated using the following abbreviations as well as their combinations: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad signal, coupling constants in Hz. Elemental analysis was carried out on Euro EA 3000 elemental analyser and the results are in agreement with the structures assigned. Microwave experiments were carried out in an Anton-Paar Monowave 300 synthesizer using borosilicate glass G10 vial sealed with PTFE-coated silicone septum. The control of reaction temperature was monitored by ruby thermometer. Mass spectra were recorded on a Shimadzu GC-MS-QP-2010 mass spectrometer in ESI (70eV) model using direct inlet probe technique and *m/z* is reported in atomic units per elementary charge. Solvents were evaporated with a Büchi rotary evaporator. Purification was performed by column chromatography using silica gel 40-63 µm (230-400 mesh size), and borosil glass column having a length about 1000 mm.

2-Butyl-5-nitrobenzo[*b*]furan (**2**). A mixture of 2-hydroxy-5-nitrobenzyl bromide **1** (5.0 g, 21.5 mmol), triphenylphosphine (5.65 g, 21.5 mmol) and dichloromethane (80 mL) was heated to reflux for 1 h. On cooling to rt, a white precipitate of phosphonium bromide salt separated. To the phosphonium bromide in toluene (100 mL), was added triethylamine (7.5 mL, 53 mmol) and pentanoyl chloride (5.19 g, 43 mmol). The mixture was heated and stirred under reflux for 3 h. After completion of the reaction (checked by TLC), It was allowed to cool, the triphenylphosphine oxide formed was filtered off, and washed with EtOAc and the filtrate was concentrated *in vacuo*. The viscous residue obtained is dissolved in water and extracted with EtOAc. The combined organic layers was dried over anhydrous Na_2SO_4 and the solvent removed to provide 2-butyl-5-nitrobenzo[*b*]furan (**2**) as a light yellow liquid. [$C_{12}H_{13}NO_3$; bp.: 318-320 ^{o}C (760 mmHg); Yield: 4.5 g, 94%].

(2-Butyl-5-nitrobenzo[*b*]furan-3-yl)(4-hydroxyphenyl)methanone (**3**). 2-Butyl-5-nitrobenzo[*b*]furan **2** (4.5 g, 20.5 mmol), 4-hydroxybenzoyl chloride (3.84 g, 24.6 mmol) and dichloromethane (40 mL) were stirred together to obtain a homogeneous solution. The flask was cooled in an ice-bath and $SnCl_4$ (4.8 mL, 41.0 mmol) was added dropwise, with stirring. The mixture was stirred for 30 min with ice cooling and then for 2 h at rt. After completion of the reaction (checked on TLC), the mixture was poured into ice cold water and extracted

with CH_2Cl_2 (20 mL × 2). The organic layer washed with saturated aq. $NaHCO_3$ (30 mL × 2). The combined organic layer was dried over anhydrous Na_2SO_4 and the solvent was removed in a Büchi evaporator to obtain a crude solid, titurated with Et_2O (10 mL × 3) to obtain (2-butyl-5-nitrobenzo[*b*]furan-3-yl)(4-hydroxy-phenyl)methanone (**3)** as a white solid. [$C_{18}H_{15}NO_5$; mp.: 91-93 °C; Yield: 5.9 g, 88%]. ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.58 (s, 1H), 8.25 (d, *J* 7.6 Hz, 2H), 7.92 (d, *J* 8.4 Hz, 1H), 7.74 (d, *J* 8.0 Hz, 2H), 6.92 (d, *J* 8.4 Hz, 2H), 2.85 (t, *J* 7.4 Hz, 2H), 1.68 (t, *J* 7.4 Hz, 2H), 1.23 (t, *J* 7.4 Hz, 2H), 0.81 (t, *J* 7.2 Hz, 3H); MS: *m/z* (M^+) 339; Anal. Calc. for $C_{19}H_{17}NO_5$: C, 67.25; H, 5.05; N, 4.13; Found: C, 67.16; H, 5.01; N, 4.03%.

4-(2-Butyl-5-nitrobenzo[*b*]furan-3-carbonyl)phenyl trifluoromethanesulfonate (**4**). A mixture of (2-butyl-5-nitrobenzo[*b*]furan-3-yl)(4-hydroxyphenyl)methanone **3** (5.9 g, 17.3 mmol), pyridine (4.19 mL, 52.1 mmol) and CH_2Cl_2 (80 mL) was stirred and cooled in an ice bath. Trifluoromethanesulfonic anhydride (8.8 mL, 52.1 mmol) was added dropwise under nitrogen. The mixture was stirred for 10 min at the same temperature and then for 3 h at rt. After completion of the reaction (checked by TLC), the mixture was poured into 1N aqueous HCl (150 mL) and extracted with EtOAc (50 mL × 2). The combined organic layer was dried over anhydrous Na_2SO_4 and the solvent was removed to give 4-(2-butyl-5-nitrobenzo[*b*]furan-3-carbonyl)phenyl trifluoromethanesulfonate (**4**) as a light yellow liquid. [$C_{20}H_{16}F_3NO_7S$; bp.: 232-234 °C (760 mmHg); Yield: 7.2 g, 87%]. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.30-8.26 (m, 1H), 8.02-7.99 (m, 2H), 7.94 (d, *J* 8.8, 1H), 7.76 (t, *J* 4.4 Hz, 2H), 2.76 (t, *J* 7.6 Hz, 2H), 1.71-1.63 (m, 2H), 1.28-1.19 (m, 2H), 0.81 (t, *J* 6.6 Hz, 3H); MS**:** *m/z* (M^+) 471; Anal. Calc. for $C_{20}H_{16}F_3NO_7S$: C, 50.96; H, 3.42; N, 2.97; Found: C, 50.81; H, 3.35; N, 2.84%.

General procedure for synthesis of (2-butyl-5-nitrobenzo[*b*]furan-3-yl)[4-(substituted ethynyl)phenyl]-methanones (**5a-k**)

Microwave irradiation (MW) method. In a 10 mL dry microwave glass vial were placed 4-(2-butyl-5-nitrobenzo[*b*]furan-3-carbonyl)phenyl trifluoromethanesulfonate (**4**) (150 mg, 0.31 mmol), Cu(Xantphos)I (48 mg, 0.06 mmol), DIPEA (0.19 mL, 1.11 mmol), DMF (5 mL) and the acetylene substrate (0.63 mmol). The mixture was degassed by purging with N_2 gas for 20 min and then bis(triphenylphosphine)palladium(II)-dichloride was added as catalyst, with further degassing for 10 min. The vial was sealed, placed in the microwave chamber and stirred at 600 rpm, 70-80 W and at 110 °C for 5-10 min. The reaction mixture was then cooled to rt, then the vial was opened and completion of reaction was checked by TLC. The reaction mass was poured into ice-cold water (20 mL) and extracted with EtOAc (20 mL × 2), the organic layer was washed with brine (25 mL × 2). The combined organic layer was dried over anhydrous Na_2SO_4 and the solvent was removed on a Büchi evaporator to obtain a crude solid product. Purification was effected by column chromatography (silica gel) using *n*-hexane:EtOAc (9:1) as eluent to afforded pure (2-butyl-5-nitrobenzo[*b*]furan-3-yl)[4-(substituted ethynyl)phenyl]methanones **5a-k**.

Conventional heating (CH) method. In a 10 mL glass vial was added 4-(2-butyl-5-nitrobenzo[*b*]furan-3-carbonyl)phenyl trifluoromethanesulfonate (**4**) (150 mg, 0.31 mmol), Cu(Xantphos)I (48 mg, 0.06 mmol), DIPEA (0.19 mL, 1.11 mmol), DMF (5 mL), and the acetylene substrate (0.63 mmol). The mixture was degassed by purging with N_2 gas for 20 min then bis(triphenylphosphine)palladium(II)dichloride was added as co-catalyst, with further degassing for 10 min. The mixture was stirred at 110 °C for 10 min. The reaction mixture was then cooled to rt and completion of reaction was checked by TLC. The mixture was poured into ice cold water (20 mL) and extracted with EtOAc (20 mL × 2), the organic layer was washed with brine (25 mL × 2). The combined organic layer was dried on anhydrous Na_2SO_4 and the solvent was removed to give a crude solid product. Purification of the crude solid was carried out by column chromatography using *n*-hexane:EtOAc (9:1) as eluent system to afford pure (2-butyl-5-nitrobenzo[*b*]furan-3-yl)[4-(substituted ethynyl)phenyl]methanones **5a-k**.

(2-Butyl-5-nitrobenzo[*b*]furan-3-yl)[4-(*p*-tolylethynyl)phenyl]methanone (**5a**). Light yellow solid; Yield: MW 79%; mp.: 79-81 °C; IR (KBr, ν_{max}, cm^{-1}): 3107 ($\nu_{C=C}$ aromatic), 2951 (ν_{C-H} aliphatic), 2210 ($\nu_{C\equiv C}$, disubstituted), 1637 ($\nu_{C=O}$), 1597 ($\nu_{C=C}$ aromatic), 1519 (ν_{NO_2} asymmetric), 1450 ($\nu_{C=C}$ aromatic), 1404 (δ_{C-H}), 1342 (ν_{NO_2} symmetric), 1265 ($\nu_{=C-O-C}$ asymmetric), 1057 ($\nu_{=C-O-C}$ symmetric), 1082 (δ_{C-H} aromatic), 810 (δ_{CH} *p*-disubstituted aromatic); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.39 (d, *J* 2.0 Hz, 1H), 8.24 (dd, *J* 2.4, 9.2 Hz, 1H), 7.81 (d, *J* 8.4 Hz, 2H), 7.66 (d, *J* 8.4 Hz, 2H), 7.58 (d, *J* 9.2 Hz, 1H), 7.47 (d, *J* 8.0 Hz, 2H), 7.19 (d, *J* 8.0 Hz, 2H), 2.90 (t, *J* 15.6 Hz, 2H), 2.39 (s, 3H), 1.75 (qt, *J* 7.6, 14.8 Hz, 2H), 1.35 (qt, *J* 7.6, 14.8 Hz, 2H), 0.90 (t, *J* 14.8 Hz, 3H); MS: *m/z* [M^+] 437; LC-MS: RT: 1.486 min., 100%; Anal. Calc. for $C_{28}H_{23}NO_4$: C, 76.87; H, 5.30; N, 3.20; Found: C, 76.84; H, 5.25; N, 3.17%.

(2-Butyl-5-nitrobenzo[*b*]furan-3-yl){4-[(2-fluorophenyl)ethynyl]phenyl}methanone (**5b**). White solid; Yield: MW 83%, CH 3%; mp.: 77-79 °C; IR (KBr, ν_{max}, cm^{-1}): 3101 (ν_{C-H} aromatic), 2955 (ν_{C-H} aliphatic), 2218 ($\nu_{C\equiv C}$, disubstituted), 1651 ($\nu_{C=O}$), 1595 ($\nu_{C=C}$ aromatic), 1531 (ν_{NO_2} asymmetric) 1448 ($\nu_{C=C}$ aromatic), 1402 (δ_{C-H}), 1342 (ν_{NO_2} symmetric), 1255 ($\nu_{=C-O-C}$ asymmetric), 1057 ($\nu_{=C-O-C}$ symmetric), 1080 (δ_{C-H} aromatic), 842 (ν_{C-F}), 756 (δ_{CH} *o*-disubstituted aromatic); ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.27 (d, *J* 10.8 Hz, 2H), 7.93 (d, *J* 8.8 Hz, 1H), 7.87 (d, *J* 8.0 Hz, 2H), 7.77 (d, *J* 7.6 Hz, 2H), 7.69 (t, *J* 6.6 Hz , 1H), 7.53 (d, *J* 5.6 Hz, 1H), 7.38 (t, *J* 9.0 Hz, 1H), 2.82 (t, *J* 7.0 Hz, 2H), 1.68 (t, *J* 6.8 Hz, 2H), 1.24 (qt, *J* 6.8, 13.6 Hz, 2H), 0.799 (t, *J* 7.0 Hz, 3H); ^{13}C-NMR (101 MHz, DMSO-d_6): δ 189.5, 168.1, 163.1, 160.6, 155.9, 144.2, 138.1, 133.6, 131.8, 131.6, 129.2, 127.0, 126.4, 124.9, 124.9, 120.6, 117.0, 116.4, 115.9, 115.7, 112.3, 110.1, 110.0, 93.3, 85.6, 29.1, 27.5, 21.6, 13.3; MS: *m/z* [M^+] 441; LC-MS: RT: 2.689 min., 100%; Anal. Calc. for $C_{22}H_{20}FNO_4$: C, 73.46; H, 4.57; N, 3.17; Found: C, 73.42; H, 4.52; N, 3.14%.

(2-Butyl-5-nitrobenzo[*b*]furan-3-yl)[4-(phenylethynyl)phenyl]methanone (**5c**). White solid; Yield: MW 88%, CH 4%; mp.**:** 81-83 °C; IR (KBr, ν_{max}, cm^{-1}): 3103 (ν_{C-H} aromatic), 2955 (ν_{C-H} aliphatic), 2214 ($\nu_{C\equiv C}$, disubstituted), 1647 ($\nu_{C=O}$), 1599 ($\nu_{C=C}$ aromatic), 1523 (ν_{NO_2} asymmetric), 1448 ($\nu_{C=C}$ aromatic), 1402 (δ_{C-H}), 1340 (ν_{NO_2} symmetric), 1253 ($\nu_{=C-O-C}$ asymmetric), 1064 ($\nu_{=C-O-C}$ symmetric), 1080 (δ_{C-H} aromatic); ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.27 (d, *J* 9.2 Hz, 2H), 7.94 (d, *J* 8.8 Hz, 1H), 7.86 (d, *J* 7.2 Hz, 2H), 7.76 (d, *J* 7.6 Hz, 2H), 7.62 (s, 2H), 7.47 (s, 3H), 2.82 (s, 2H), 1.67 (d, *J* 6.4 Hz, 2H), 1.24 (d, *J* 6.8 Hz, 2H), 0.80 (t, *J* 6.6 Hz, 3H); ^{13}C-NMR (101 MHz, DMSO-d_6): δ 189.5, 168.1, 155.9, 144.2, 137.8, 131.7, 131.6, 129.3, 129.2, 128.8, 127.1, 127.0, 121.6, 120.6, 117.0, 116.4, 112.3, 92.5, 88.5, 29.1, 27.5, 21.6, 13.3; Ms: *m/z* [M^+] 423; Anal. Calc. for $C_{27}H_{21}NO_4$: C, 76.58; H, 5.00; N, 3.31; Found: C, 76.54; H, 4.98; N, 3.23%.

(2-Butyl-5-nitrobenzo[*b*]furan-3-yl)){4-[(4-propylphenyl)ethynyl]phenyl}methanone (**5d**). Off white solid; Yield: MW 81%, CH 3%; mp.: 79-81 °C; IR (KBr, ν_{max}, cm^{-1}): 3107 (ν_{C-H} aromatic), 2958 (ν_{C-H} aliphatic), 2208 ($\nu_{C\equiv C}$, disubstituted), 1633 ($\nu_{C=O}$), 1595 ($\nu_{C=C}$ aromatic), 1525 (ν_{NO_2} asymmetric), 1450 ($\nu_{C=C}$ aromatic), 1404 (δ_{C-H}), 1346 (ν_{NO_2} symmetric), 1263 ($\nu_{=C-O-C}$ asymmetric) 1053 ($\nu_{=C-O-C}$ symmetric), 1084 (δ_{C-H} aromatic), 833 (δ_{CH} *p*-disubstituted aromatic); ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.26 (t, *J* 5.6 Hz, 2H), 7.94 (d, *J* 8.8 Hz, 1H), 7.85 (d, *J* 8.0 Hz, 2H), 7.74 (d, *J* 8.4 Hz, 2H), 7.52 (d, *J* 8.0 Hz, 2H), 7.28 (d, *J* 8.0 Hz, 2H), 2.83 (t, *J* 7.6 Hz, 2H), 2.59 (t, *J* 7.6 Hz, 2H), 1.72-1.56 (m, 4H), 1.29-1.19 (m, 2H), 0.89 (t, *J* 7.2 Hz, 3H), 0.80 (t, *J* 7.4 Hz, 3H); ^{13}C-NMR (101 MHz, DMSO-d_6): δ 189.5, 168.0, 155.9, 144.2, 143.8, 137.6, 131.6, 131.5, 129.2, 128.8, 127.2, 127.1, 120.6, 118.9, 117.0, 116.4, 112.3, 92.8, 88.0, 37.1, 29.1, 27.5, 23.8, 21.6, 13.6, 13.3; Ms: *m/z* [M^+] 465; Anal. Calc. for $C_{30}H_{27}NO_4$: C, 77.40; H, 5.85; N, 3.01; Found: C, 77.36; H, 5.81; N, 2.97%.

(2-Butyl-5-nitrobenzo[*b*]furan-3-yl)){4-[((4-fluorophenyl)ethynyl]phenyl}methanone (**5e**). White solid; Yield: MW 85%, CH 3%; mp.: 69-71 °C; IR (KBr, ν_{max}, cm^{-1}): 3091 ($\nu_{C=C}$ aromatic), 2951 (ν_{C-H} aliphatic), 2218 ($\nu_{C\equiv C}$, disubstituted), 1639 ($\nu_{C=O}$), 1593 ($\nu_{C=C}$ aromatic), 1516 (ν_{NO_2} asymmetric), 1450 ($\nu_{C=C}$ aromatic), 1402 (δ_{C-H} aromatic), 1346 (ν_{NO_2} symmetric), 1259 ($\nu_{=C-O-C}$ asymmetric), 1051 ($\nu_{=C-O-C}$ symmetric), 1078 (δ_{C-H} aromatic), 972 (ν_{C-F}), 848 (δ_{CH} *p*-disubstituted aromatic); ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.27 (d, *J* 8.8 Hz, 2H), 7.94 (d, *J* 8.8

Hz, 1H), 7.86 (d, *J* 8.0 Hz, 2H), 7.75 (d, *J* 7.6 Hz, 2H), 7.69 (t, *J* 6.4 Hz, 2H), 7.31 (t, *J* 8.4 Hz, 2H), 2.83 (t, *J* 7.0 Hz, 2H), 1.68 (t, *J* 7.0 Hz, 2H), 1.25 (qt, *J* 7.2, 14.4 Hz, 2H), 0.81 (t, *J* 7.2 Hz, 3H); ^{13}C-NMR (101 MHz, DMSO-d_6): δ 189.5, 168.1, 163.6, 161.1, 155.9, 144.2, 137.8, 134.0, 133.9, 131.7, 129.2, 127.1, 126.8, 120.6, 118.1, 118.1, 117.0, 116.4, 116.2, 116.0, 112.3, 91.5, 88.2, 29.1, 27.5, 21.6, 13.3; MS: *m/z* [M$^+$] 441; Anal. Calc. for $C_{27}H_{20}FNO_4$: C, 73.46; H, 4.57; N, 3.17; Found: C, 73.40; H, 4.52; N, 3.16%.

(2-Butyl-5-nitrobenzo[*b*]furan-3-yl)[4-(cyclopropylethynyl)phenyl]methanone (**5f**). Yellow liquid; Yield: MW 91%, CH 6%; bp.: 228-230 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.24 (dd, *J* 2.4, 8.0 Hz, 2H), 7.91 (dd, *J* 2.4, 7.6 Hz, 1H), 7.75 (dd, *J* 1.6, 6.8 Hz, 2H), 7.54 (dd, *J* 2.0, 6.8 Hz, 2H), 2.79 (t, *J* 7.6 Hz, 2H), 1.69-1.57 (m, 3H), 1.27-1.17 (m, 3H), 0.96-0.915 (m, 2H), 0.86-0.80 (m, 5H); ^{13}C-NMR (101 MHz, DMSO-d_6): δ 189.5, 168.0, 156.0, 144.3, 137.0, 131.7, 129.2, 128.3, 127.2, 120.7, 117.0, 116.5, 112.4, 98.1, 75.2, 29.3, 27.6, 21.8, 13.5, 8.8; Ms: *m/z* [M$^+$] 387; Anal. Calc. for $C_{24}H_{21}NO_4$: C, 74.40; H, 5.46; N, 3.62; Found: C, 74.36; H, 5.41; N, 3.59%.

(2-Butyl-5-nitrobenzo[*b*]furan-3-yl)[4-(cyclopentylethynyl)phenyl]methanone (**5g**). Yellow liquid; Yield: MW 90%, CH 7%; bp.: 224-226 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.24 (d, *J* 2.4 Hz, 1H), 8.22 (d, = 2.4 Hz, 1H), 7.90 (d, *J* 10.0 Hz, 1H), 7.75 (d, *J* 8.4 Hz, 2H), 2.54 (d, *J* 8.0 Hz, 2H), 2.92-2.77 (m, 3H), 2.01-1.96 (m, 2H), 1.74-1.55 (m, 8H), 1.24-1.19 (m, 2H), 0.78 (t, *J* 7.4 Hz, 3H) ; ^{13}C-NMR (101 MHz, DMSO-d_6): δ 189.4, 167.8, 155.9, 144.1, 137.0, 131.5, 129.0, 128.2, 127.1, 120.5, 116.9, 116.4, 112.2, 98.6, 79.5, 72.6, 33.3, 33.1, 30.1, 29.6, 27.5, 24.6, 24.5, 24.5, 22.9, 21.6, 13.3; MS: *m/z* [M$^+$] 415; Anal. Calc. for $C_{26}H_{25}NO_4$: C, 75.16; H, 6.07; N, 3.37; Found: C, 75.11; H, 6.01; N, 3.34%.

(2-Butyl-5-nitrobenzo[*b*]furan-3-yl)[4-(cyclohexylethynyl)phenyl]methanone (**5h**). Yellow liquid; Yield: MW 87%, CH 5%; bp.: 231-233 °C; IR (KBr, ν_{max}, cm^{-1}): 3103 (ν_{C-H} aromatic), 2928 (ν_{C-H} aliphatic), 2224 ($\nu_{C\equiv C}$ disubstituted), 1645 ($\nu_{C=O}$), 1599 ($\nu_{C=C}$ aromatic), 1531 (ν_{NO_2} asymmetric), 1448 ($\nu_{C=C}$ aromatic), 1402 (δ_{C-H}), 1344 (ν_{NO_2} symmetric), 1251 ($\nu_{=C-O-C}$ asymmetric), 1053 ($\nu_{=C-O-C}$ symmetric), 1082 (δ_{C-H} aromatic); ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.27-8.25 (m, 2H), 7.94 (d, *J* 10.0 Hz, 1H), 7.78 (d, *J* 8.4 Hz, 2H), 7.57 (d, *J* 8.4 Hz, 2H), 2.81 (t, *J* 7.6 Hz, 2H), 2.70 (t, *J* 3.6 Hz, 1H), 1.86 (t, *J* 4.8 Hz, 2H), 1.70-1.63 (m, 4H), 1.54-1.47 (m, 4H), 1.40-1.33 (m, 4H), 1.28-1.20 (m, 2H), 0.80 (t, *J* 7.4 Hz, 3H); MS: *m/z* [M$^+$] 429; Anal. Calc. for $C_{27}H_{27}NO_4$: C, 75.50; H, 6.34; N, 3.26; Found: C, 75.43; H, 6.28; N, 3.22%.

(2-Butyl-5-nitrobenzo[*b*]furan-3-yl)[4-(hept-1-yn-1-yl)phenyl)]methanone (**5i**). White liquid; Yield: MW 93%, CH 8%; bp.: 216-218 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.25 (dd, *J* 2.4, 6.0 Hz, 2H), 7.93 (dd, *J* 3.6, 6.0 Hz, 1H), 7.78 (d, *J* 8.0 Hz, 2H), 7.57 (d, *J* 8.0 Hz, 2H), 2.80 (t, *J* 7.4 Hz, 2H), 2.48 (t, *J* 7.0 Hz, 2H), 1.71-1.63 (m, 2H), 1.61-1.54 (m, 2H), 1.45-1.31 (m, 4H), 1.29-1.19 (m, 3H), 0.90 (t, *J* 7.0 Hz, 3H), 0.80 (t, *J* 7.4 Hz, 3H); ^{13}C-NMR (101 MHz, DMSO-d_6): δ 189.4, 167.9, 155.9, 144.2, 137.1, 131.5, 129.1, 128.1, 127.1, 120.6, 116.90, 116.4, 112.2, 94.7, 80.0, 30.5, 29.1, 27.7, 27.5, 21.6, 18.7, 13.8, 13.3; MS: *m/z* [M$^+$] 417; Anal. Calc. for $C_{26}H_{27}NO_4$: C, 74.80; H, 6.52; N, 3.35; Found: C, 74.73; H, 6.52; N, 3.31%.

(2-Butyl-5-nitrobenzo[*b*]furan-3-yl))[4-[(4-ethylphenyl)ethynyl)]phenyl}methanone (**5j**). Yellow solid; Yield: MW 81%, CH 8%; mp.: 60-62 °C; IR (KBr, ν_{max}, cm^{-1}): 3101 (ν_{C-H} aromatic), 2922 (ν_{C-H} aliphatic), 2212 ($\nu_{C\equiv C}$, disubstituted), 1653 ($\nu_{C=O}$), 1597 ($\nu_{C=C}$ aromatic), 1531 (ν_{NO_2} asymmetric), 1450 ($\nu_{C=C}$ aromatic), 1404 (δ_{C-H}), 1342 (ν_{NO_2} symmetric), 1253 ($\nu_{=C-O-C}$ asymmetric), 1055 ($\nu_{=C-O-C}$ symmetric), 1080 (δ_{C-H} aromatic); ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.28 (s, 1H), 8.25 (d, *J* 2.0 Hz, 1H), 7.93 (d, *J* 8.4 Hz, 1H), 7.85 (d, *J* 8.0 Hz, 2H), 7.74 (t, *J* 7.6 Hz, 2H), 7.52 (d, *J* 8.0 Hz, 1H), 7.29 (t, *J* 9.4 Hz, 2H), 2.82 (t, *J* 7.6 Hz, 2H), 2.65 (qt, *J* 7.6, 22.8 Hz, 2H), 1.71-1.64 (m, 2H), 1.28-1.17 (m, 5H), 0.80 (t, *J* 7.4 Hz, 3H); ^{13}C-NMR (101 MHz, DMSO-d_6): δ 189.5, 168.0, 155.9, 145.4, 137.6, 131.6, 129.2, 128.3, 127.2, 127.1, 120.6, 118.9, 116.9, 116.4, 112.3, 92.8, 88.0, 29.1, 28.1, 27.5, 21.6, 15.2, 13.3; MS: *m/z* [M$^+$] 451; Anal. Calc. for $C_{29}H_{25}NO_4$: C, 77.14; H, 5.58; N, 3.10; Found: C, 77.10; H, 5.54; N, 3.06%.

(2-Butyl-5-nitrobenzo[*b*]furan-3-yl)(4-ethynylphenyl)methanone (**5k**). off-white solid; Yield: MW 94%, CH 10%; mp.: 82-84 °C; IR (KBr, ν_{max}, cm^{-1}): 3255 ($\nu_{\equiv C-H}$), 3107 (ν_{C-H} aromatic), 2953 (ν_{C-H} aliphatic), 2158 ($\nu_{C\equiv C}$, monosubstituted), 1639 ($\nu_{C=O}$), 1564 ($\nu_{C=C}$ aromatic), 1523 (ν_{NO_2} asymmetric), 1450 ($\nu_{C=C}$ aromatic), 1346 (ν_{NO_2} symmetric), 1249 ($\nu_{=C-O-C}$ asymmetric), 1055 ($\nu_{=C-O-C}$ symmetric), 1082 (δ_{C-H} aromatic); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.13 (d, *J* 2.0 Hz, 1H), 8.01 (dd, *J* 2.4, 9.2 Hz, 1H), 7.54 (dd, *J* 1.6, 6.4 Hz, 2H), 7.38 (dd, *J* 2.0, 6.8 Hz, 3H), 2.66 (t, *J* 7.6 Hz, 2H), 1.57-1.49 (m, 2H), 1.16-1.02 (m, 3H), 0.67 (t, *J* 7.2 Hz, 3H); Ms: *m/z* [M^+] 347; Anal. Calc. for $C_{21}H_{17}NO_4$: C, 72.61; H, 4.93; N, 4.03; Found: C, 72.55; H, 4.88; N, 3.99%.

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Supplementary Material

Copies of Mass, IR, ^{1}H NMR, ^{13}C NMR and LC-MS spectra of synthesized compounds are available in the Supplementary Material.

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