# Bioisosteric Replacement of the Pyrazole 5-Aryl Moiety of *N*-(Piperidin-1-yl)-5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-4-methyl-1*H*-pyrazole-3-carboxamide (SR141716A). A Novel Series of Alkynylthiophenes as Potent and Selective Cannabinoid-1 Receptor Antagonists

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Replacing the conventional pyrazole 5-aryl substituent of **1** (SR141716A) with the 2-thienyl moiety appended with an appropriate alkynyl unit, a novel class of 5-(5-alkynyl-2-thienyl)pyrazole derivatives, behaving as highly potent CB1 receptor antagonists with good CB1/2 selectivity, was discovered, many of which, as typified by compound **18**, showed significant weight reduction in diet-induced obese mouse model, thus pharmacologically validating that the bioisosteric replacement described above is viable. Also encouraging was the finding that a subtle structural modification of the newly developed series could result in a distinct difference in the intrinsic property, as demonstrated by compounds **12** (NA) and its methylated structural isomers **15** (PA) and **18** (IA). Moreover, current structure−activity relationship studies revealed that around the pyrazole 5-position of **1**, a deep and flat crevice surrounded by a sequence of hydrophobic/aromatic residues as indicated by the CB1-receptor homology model might exist in the binding site.

## Introduction

The prevalence of obesity has been increasing dramatically during the past 3 decades, mainly resulting from the profound changes in society and the behavioral patterns as a consequence of increasing industrialization and sedentary lifestyles along with energy-rich diets. Obesity has become a widespread epidemic and is recognized as one of the top 10 global health problems by World Health Organization. Considerable evidence discloses that individuals with excess body fat are faced with an increasing risk of mortality and comorbidities, including coronary heart diseases, type 2 diabetes, and some forms of cancer.[1] While substantial efforts have been made in the area of weight regulation, only two antiobesity agents orlistat and sibutramine, serving as a gastrointestinal lipase inhibitor to reduce fat absorption and an appetite suppressant by inhibiting reuptake of serotonin and noradrenaline, respectively, have been successfully marketed for the long-term obesity treatment in recent years. However, owing to their limited efficacy in weight reduction and significant accompanying adverse effects, these pharmacological approaches have only met with moderate success. Therefore, pursuing a new generation of antiobesity therapeutics acting on novel molecular targets, such as cannabinoid-1 receptors (CB1),[2] 5-hydroxytryptamine 2C receptors (5-HT2C),[3] melanocortin-4 receptors (MC4R),[4] and melanin-concentrating hormone-1 receptors (MCHR-1),[5] to improve the unmet pharmacological effects and safety profiles remains an urgent medical need. Along these lines, the first successful clinical candidate **1** (SR141716A, rimonabant, Figure 1),[6] which behaves as a selective CB1 inverse agonist with transmittance of a satiety signal to the brain before meals, resulting in appetite suppression and limiting food intake,[7,8] was discovered and launched in Europe in 2006.[9] Compound **1** was first approved for the treatment of obese or overweight patients with the related metabolic syndrome.[10−12] However, in addition to presenting a major indication for weight reduction, CB1 receptor antagonists[13] also show great promise in many potential therapeutic applications including type 2 diabetes (phase III),[14] atherosclerosis (phase III),[15] smoking addiction (phase III),[16] alcoholism (phase II),[17] drug dependence,[18] cognitive disorders,[19] liver cirrhosis,[20] inflammation and arthritis,[21] etc., several of which are in advanced clinical trials, suggesting that CB1 receptor might become a versatile drug target.

Since compound **1** was identified as the first potent and selective CB1 antagonist from 1994, a wide variety of new mimetics, mainly generated by replacing the central pyrazole skeleton with analogous heteroaromatic rings, have been designed,[22] and such molecular modifications, in many historical cases, have met with success in offering significant bioisosteres.[23,24] In contrast, limited efforts have been devoted to the modification of the pyrazole-C5 position of **1** (Figure 1).[25] In order to investigate the pharmacological effects exerted by the C5 substitution, a strategy of bioisosterism[26] was then applied to generate the following novel rimonabant-mimicking molecules. Accordingly, the vinylene unit (−CH═CH−) or imine group (−CH═N−) in the aromatic rings of drug molecules could be replaced with a "ring equivalent" such as the sulfur (S), oxygen (O), selenium (Se), or NH group, resulting in the corresponding heterocyclic rings with equivalent steric and electronic characteristics. As such, the thiophene ring, being recognized as the most druglike and popular bioisostere of the phenyl ring,[26e] was adopted as the initial model to test this concept. As a result, novel compound **1** analogues, specifically characterized with an alkynyl linker on the pyrazole-C5 thiophene ring, were discovered, many of which were found to behave as potent CB1 receptor antagonists[13] with good CB2/1 selectivity, validating the bioisosteric hypothesis that the C5 phenyl ring could be replaced with an appropriately substituted thiophene moiety.

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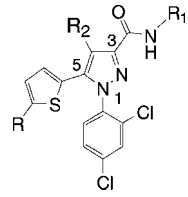
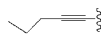
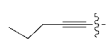
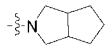
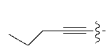
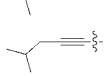
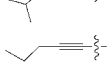
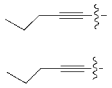
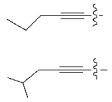
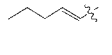
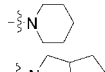
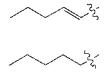
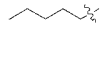
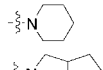
**Table 1.** Biological Evaluation of Novel 5-Thiophen-2-ylpyrazole Derivatives on hCB1 and hCB2 Receptors



| Compound | R | $R_1$ | $R_2$ | $IC_{50}$ (nM)[a,c] hCB1 | $IC_{50}$ (nM)[a,c] hCB2 | $EC_{50}$ (nM)[b,c] | Selectivity CB2/CB1 | Intrinsic Property[d] |
|---|---|---|---|---|---|---|---|---|
| **6** | Br |  | Me | 35.8 ± 17.0 | 894.6 ± 248.4 | 68.2 ± 12.3 | 25 | IA |
| **7** | Br |  | Me | 40.7 ± 9.5 | 704.9 ± 104.7 | 64.9 ± 8.6 | 17 | IA |
| **8** | Cl |  | Me | 50.2 ± 17.3 | 1291.4 ± 371.9 | 146.5 ± 51.4 | 26 | IA |
| **9** | Cl |  | Me | 158.7 ± 36.8 | 2156.1 ± 368.1 | 133.9 ± 54.7 | 14 | IA |
| **12** |  |  | Me | 13.9 ± 4.4 | 2214.0 ± 452.2 | 28.7 ± 7.5 | 159 | NA |
| **13** |  |  | Me | 7.9 ± 1.4 | 785.1 ± 83.9 | 19.2 ± 7.6 | 99 | NA |
| **14** |  |  | Me | 7.0 ± 2.0 | 1499.2 ± 213.1 | 14.1 ± 3.8 | 214 | NA |
| **15** |  |  | Me | 2.3 ± 0.5 | 385.9 ± 142.7 | 12.1 ± 5.8 | 168 | PA |
| **16** |  |  | Me | 4.9 ± 2.9 | 687.7 ± 257.5 | 14.6 ± 4.9 | 139 | PA |
| **18** |  |  | Et | 6.1 ± 2.6 | 919.6 ± 53.1 | 13.8 ± 4.4 | 151 | IA |
| **19** |  |  | Et | 8.9 ± 2.6 | 303.9 ± 50.1 | 16.5 ± 4.4 | 34 | IA |
| **20** |  |  | Et | 5.1 ± 0.9 | 1206.0 ± 283.6 | 23.0 ± 1.9 | 236 | IA |
| **21** |  |  | Me | 21.6 ± 4.4 | 3838.3 ± 492.3 | 146.2 ± 77.1 | 178 | IA |
| **22** |  |  | Me | 27.5 ± 6.6 | 5412.8 ± 1469.4 | 71.4 ± 14.1 | 197 | IA |
| **23** |  |  | Me | 57.9 ± 17.4 | 6346.0 ± 1484.9 | 75.9 ± 16.1 | 109 | IA |
| **24** |  |  | Me | 20.6 ± 6.2 | 3664.3 ± 446.8 | 48.0 ± 6.4 | 178 | IA |
| **Compound 1** | | | | 15.0 ± 1.8 | 1939.8 ± 131.1 | 18.2 ± 9.5 | 129 | IA |

[a] Binding affinity determined by inhibition of [$^3$H]-CP55940 ([$^3$H]-**49**) binding to hCB1- or hCB2-transfected HEK 293 membrane is expressed as $IC_{50}$. [b] Functional activity determined by inhibition of Eu-GTP binding to hCB1-transfected HEK 293 membrane is expressed as $EC_{50}$. [c] Data are expressed as the mean ± SD of at least three independent experiments. [d] According to the definition reported in the literature,[36] the intrinsic property of each compounds is identified as an IA, NA, or PA as assessed by the Eu-GTP biding to hCB1-transfected HEK 293 membrane (see Figure 4).

Detailed description on the design, synthesis, and SAR[a] of these newly developed molecules will be presented as follows.

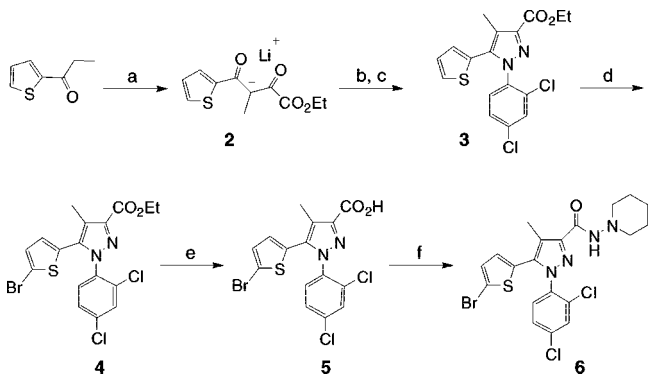
## Chemistry

Compounds **6**−**9** in Table 1 were prepared according to a general synthetic method shown in Scheme 1 using compound **6** as a typical example. Treatment of 1-(thiophen-2-yl)propan-1-one with diethyl oxalate in the presence of LHMDS as a base gave rise to lithium salt **2** in 85% yield, which in turn was allowed to couple with 2,4-dichlorophenylhydrazine hydrochloride in ethanol followed by intramolecular cyclization under refluxing acetic acid to provide ester **3** in 50% yield over two steps. Regioselective bromination of ester **3** was smoothly effected using NBS in acetonitrile to afford the corresponding 5-bromo ester **4** in excellent yield (95%). Compound **4** thus obtained was subjected to basic hydrolysis under standard conditions to give carboxylic acid **5** in 96% yield, which was then treated with trimethylacetyl chloride to activate the carboxylic group followed by coupling with 1-aminopiperidine to furnish the desired product **6** in 71% yield.

Compounds **12**−**16**, **21**, **22**, and **25**−**42** were readily prepared via a synthetic sequence Scheme 2 using compound **4** as the starting material. Taking product **12** as a specific target, intermediate **4** was first coupled with 1-pentyne in the presence of $Pd(PPh_3)_2Cl_2$ and CuI as catalyst to give ester **10** in 94% yield.[27] Subsequent hydrolysis of compound **10** under basic conditions resulted in the formation of carboxylic acid **11** in quantitative yield (96%), which in turn was converted to the desired amide **12** through a two-step sequence in 73% yield, involving activation of the carboxyl group with trimethylacetyl chloride followed by amidation with 1-aminopiperidine. Compounds **18**−**20**, where an ethyl group was introduced at the

[a] Abbreviations: SAR, structure−activity relationship; CB, cannabinoid; LHMDS, lithium bis(trimethylsilyl)amide; NBS, *N*-bromosuccinimide; Eu-GTP, europium guanosine 5′-triphosphate; NA, neutral antagonist; PA, partial agonist; IA, inverse agonist; DIO, diet-induced obese.

**Scheme 1**[a]



[a] Reagents and conditions: (a) LHMDS, diethyl oxalate, THF/$Et_2O$ (2/1), −78 °C to room temp, 20 h, 85%; (b) 2,4-dichlorophenylhydrazine hydrochloride, EtOH, room temp, 22 h; (c) AcOH, 120 °C, 24 h, 50% over two steps; (d) NBS, $CH_3CN$, 0 °C to room temp, 16 h, 95%; (e) KOH, MeOH, reflux, 3 h, 96%; (f) trimethylacetyl chloride, $Et_3N$, $CH_2Cl_2$, 0 °C to room temp, 2 h, then 1-aminopiperidine, $Et_3N$, 0 °C to room temp, 2 h, 71%.

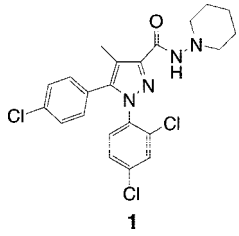


**Figure 1.** Structure of the first launched CB1 inverse agonist.

pyrazole C4-position, were readily prepared following a similar synthetic sequence as described for compounds **12**, **14**, and **15**, respectively, with the exception that 1-(thiophen-2-yl)butan-1-one instead of 1-(thiophen-2-yl)propan-1-one was used as the starting material. In a similar fashion, the corresponding alkenyl compounds **21** and **22** were also successfully synthesized following Scheme 2 except that Suzuki coupling reaction,[28] instead of Sonogashira reaction, was employed as the key operation to provide the alkenyl intermediate **10b**.

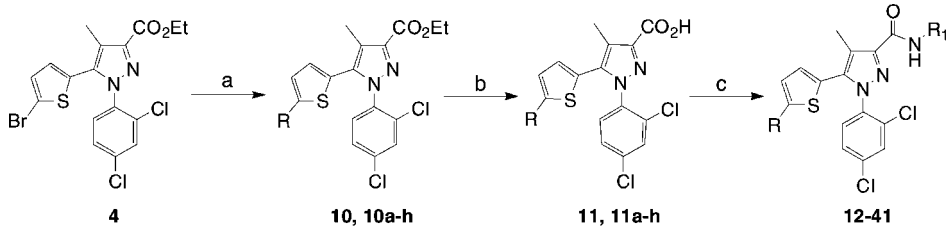
As well, for comparison purposes, in parallel to alkynyl compounds **12**−**13** and alkenyl analogues **21** and **22**, the saturated alkyl counterparts **23** and **24**, readily prepared by Scheme 3, were also afforded for biological evaluations. Compounds **43**−**48**, individually inserted with a heteroatom N or O in the alkynyl linker, were provided based on Scheme 4, making use of the Sonogashira reaction as a key operation. To improve water solubility, where applicable, all tested compounds were converted into the corresponding hydrochloride salts by treatment with an excess of hydrochloric acid (Aldrich, 1.0 M solution in diethyl ether) prior to submission for biological assays.

## Results and Discussion

Compounds described above were subjected to biological evaluations toward CB1 and CB2 receptors, results of which are compiled in Tables 1−3, and related SAR studies will be discussed below. The initial results with compounds **6**−**9**, bearing the highest structural similarity to rimonabant, are encouraging in that these halogenated analogues not only showed adequately high binding affinity ($IC_{50}$ = 36−158 nM) but also significant potency ($EC_{50}$ = 65−147 nM) toward CB1 receptors, indicating that they are well qualified to serve as lead compounds for further structural modifications. On the basis of the common scaffold of compounds **6**−**9** and a general CB1 inverse agonist pharmacophore model,[22a,29,30] attempts to enhance receptor−ligand interaction on the pyrazole C5 thiophene ring by replacing the halogen substituent with a variety of hydrophobic groups were then made. As a result, compounds **12**−**24** (Table 1), each appended with a commercially available aliphatic linker in place of the halogen, were first synthesized according to Schemes 2 and 3. Surprisingly, these newly developed compounds, in general, exhibited a significant improvement in almost all biological aspects, including CB1 binding affinity and functional activity as well as CB2/1 selectivity, compared to the parent leads **6**−**9**. Particularly, those analogues substituted with an alkynyl linker, such as **12**−**16**, **18**, and **20**, were found to acquire the highest binding affinity ($IC_{50}$ = 2.3−13.9 nM), potency ($EC_{50}$ = 12.1−23.0 nM), and selectivity (CB2/1 = 99−236), many of which are comparable to the reference compound **1** ($IC_{50}$ = 15.0 nM; $EC_{50}$ = 18.2 nM; CB2/1 = 129), serving constantly as the positive control at the same assay systems. As well, as demonstrated by alkynyl **12** ($IC_{50}$ = 13.9; $EC_{50}$ = 28.7 nM) and its counterparts alkenyl **21** ($IC_{50}$ = 21.6; $EC_{50}$ = 146.2 nM) and alkyl **23** ($IC_{50}$ = 57.9; $EC_{50}$ = 75.9 nM), the alkynylthiophenes appeared superior to the corresponding alkenyl- and alkylthiophenes in eliciting the receptor−ligand interactions. The similar bioactive trend was also observed with compound **13** ($IC_{50}$ = 7.9; $EC_{50}$ = 19.2 nM) and its analogues alkenyl **22** ($IC_{50}$ = 27.5; $EC_{50}$ = 71.4 nM) and alkyl **24** ($IC_{50}$ = 20.6; $EC_{50}$ = 48.0 nM), indicating that the acetylenic unit (−C≡C−) might render the alkynyl side chain a unique stereoelectronic nature and/or spatial orientation, leading to an unusual enhancement of the required hydrophobic interaction via the aromatic stacking and/or induced-dipole interaction. However, exactly what controls such a remarkable outcome for the aforementioned alkynyl system is still not fully understood and remains to be determined.[31] Moreover, it was found that a slight chemical modification in the alkynylthiophene series might result in the structurally closely related analogues with a distinct difference in the intrinsic properties. As illustrated with selected compounds **12**, **15**, and **18**, when an additional methyl group was appropriately positioned on compound **12**, originally behaving as a neutral antagonist (NA), its regioisomers **15** and **18** could be converted into a partial agonist (PA) and inverse agonist (IA), respectively. The same observation was also made on compounds **14** (NA) and its methylated analogues **16** (PA) and **19** (IA). The results presented above are quite unexpected and appealing, particularly given the hypothesis that the existence of C-3 carboxamide functionality might predominate over the production of inverse agonism in rimonabant-mimicking compounds, presumably due to the carbonyl group being able to serve as an essential hydrogen-bond acceptor to stabilize the putative Asp366-Lys192 salt bridge in the R state of the CB1 receptors.[30,32] As well, the presence of the ethyl group at pyrazole-C4 position seems to confer significant inverse agonism on the overall molecules as illustrated by compounds **18**−**20**. To confirm the generality of this finding, however, additional research with particular emphasis on synthesizing the same C4-ethyl series of the corresponding alkenyl- and alkylthiophene systems is imperative.

On the basis of these encouraging results, structurally more diverse alkynylthiophenes, primarily based on synthetic Schemes 2 and 4, were further synthesized. Compounds **25**−**47** thus generated were assayed toward CB1 receptors, results of which are listed in Tables 2 and 3. Table 2 summarizes the structure−activity relationship studies on the alkynyl linker in different dimensions, including the ring size and chain length.

**Scheme 2**[a]



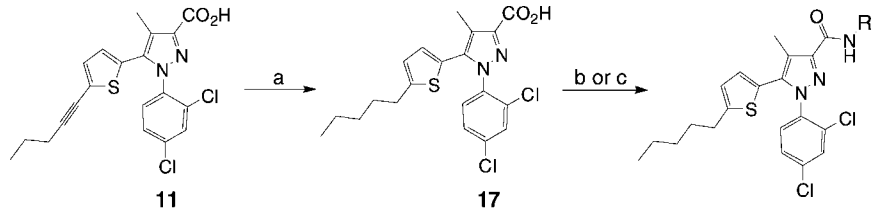

**10**: R = pent-1-ynyl
**10a**: R = 4-methylpent-1-ynyl
**10b**: R = pent-1-enyl
**10c**: R = but-1-ynyl
**10d**: R = hex-1-ynyl
**10e**: R = 3,3-dimethylbut-1-ynyl
**10f**: R = 2-cyclopropyleth-1-ynyl
**10g**: R = 2-cyclopentyleth-1-ynyl
**10h**: R = 2-cyclohexyleth-1-ynyl

**11**: R = pent-1-ynyl
**11a**: R = 4-methylpent-1-ynyl
**11b**: R = pent-1-enyl
**11c**: R = but-1-ynyl
**11d**: R = hex-1-ynyl
**11e**: R = 3,3-dimethylbut-1-ynyl
**11f**: R = 2-cyclopropyleth-1-ynyl
**11g**: R = 2-cyclopentyleth-1-ynyl
**11h**: R = 2-cyclohexyleth-1-ynyl

| | |
|---|---|
| **12**: R = pent-1-ynyl | $R_1$ = piperidinyl |
| **13**: R = pent-1-ynyl | $R_1$ = 3-azabicyclo[3.3.0]octanyl |
| **14**: R = pent-1-ynyl | $R_1$ = azepan-1-yl |
| **15**: R = 4-methylpent-1-ynyl | $R_1$ = piperidinyl |
| **16**: R = 4-methylpent-1-ynyl | $R_1$ = azepan-1-yl |
| **21**: R = pent-1-enyl | $R_1$ = piperidinyl |
| **22**: R = pent-1-enyl | $R_1$ = 3-azabicyclo[3.3.0]octanyl |
| **25**: R = but-1-ynyl | $R_1$ = piperidinyl |
| **26**: R = but-1-ynyl | $R_1$ = 3-azabicyclo[3.3.0]octanyl |
| **27**: R = but-1-ynyl | $R_1$ = azepan-1-yl |
| **28**: R = hex-1-ynyl | $R_1$ = piperidinyl |
| **29**: R = hex-1-ynyl | $R_1$ = 3-azabicyclo[3.3.0]octanyl |
| **30**: R = hex-1-ynyl | $R_1$ = azepan-1-yl |
| **31**: R = hex-1-ynyl | $R_1$ = n-butyl |
| **32**: R = hex-1-ynyl | $R_1$ = n-hexyl |
| **33**: R = hex-1-ynyl | $R_1$ = cyclohexyl |
| **34**: R = 3,3-dimethylbut-1-ynyl | $R_1$ = piperidinyl |
| **35**: R = 3,3-dimethylbut-1-ynyl | $R_1$ = 3-azabicyclo[3.3.0]octanyl |
| **36**: R = 2-cyclopropyleth-1-ynyl | $R_1$ = piperidinyl |
| **37**: R = 2-cyclopropyleth-1-ynyl | $R_1$ = 3-azabicyclo[3.3.0]octanyl |
| **38**: R = 2-cyclopentyleth-1-ynyl | $R_1$ = piperidinyl |
| **39**: R = 2-cyclopentyleth-1-ynyl | $R_1$ = 3-azabicyclo[3.3.0]octanyl |
| **40**: R = 2-cyclohexyleth-1-ynyl | $R_1$ = piperidinyl |
| **41**: R = 2-cyclohexyleth-1-ynyl | $R_1$ = 3-azabicyclo[3.3.0]octanyl |

[a] Reagents and conditions: (a) various alkynes, $Pd(PPh_3)_2Cl_2$, CuI, 2-ethanolamine, 60 °C, THF/$H_2O$ (1/1), 3 h, 92−97%. For **10b**: $Pd(PPh_3)_4$, (*E*)-pent-1-enylboronic acid, $Cs_2CO_3$, DME, 80 °C, 3 h, 75%. (b) KOH, MeOH, reflux, 3 h, 92−96%. (c) trimethylacetyl chloride, $Et_3N$, $CH_2Cl_2$, 0 °C to room temp, 2 h, then various amines, 0 °C to room temp, 2 h, 65−73%.

**Scheme 3**[a]

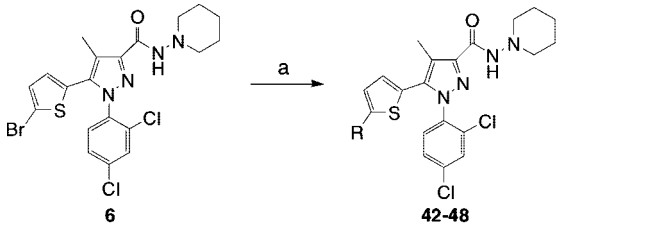



**23**: R= piperidinyl
**24**: R= 3-azabicyclo[3.3.0]octanyl

[a] Reagents and conditions: (a) $H_2$(g), 1 atm, 10% Pd/C, MeOH, room temp, 24 h, 45%; (b) trimethylacetyl chloride, $Et_3N$, $CH_2Cl_2$, 0 °C to room temp, 2 h, then 1-aminopiperidine, 0 °C to room temp, 2 h, 75% over two steps for **23**; (c) trimethylacetyl chloride, $Et_3N$, $CH_2Cl_2$, 0 °C to room temp, 2 h, then 3-aminoazabicyclo[3.3.0]octane hydrochloride, 0 °C to room temp, 2 h, 67% over two steps for **24**.

As compared with compounds **12**−**14** ($IC_{50}$ = 7.0−13.9 nM; $EC_{50}$ = 14.1−28.7 nM; CB2/1 = 99−214), when the linker was elongated with one more methylene unit, the corresponding compounds **28**−**30** ($IC_{50}$ = 1.3−1.7 nM; $EC_{50}$ = 4.8−7.9 nM; CB2/1 = 122−332) resulted in a significant increase in all biological profiles. Indeed, in all alkynyl cases examined, they are the most potent chemical entities with excellent CB2/1 selectivity. Conversely, when the chain length was decreased by one methylene unit as illustrated with compounds **25**−**27** ($IC_{50}$ = 24.2−65.4 nM; $EC_{50}$ = 35.5−51.4 nM; CB2/1 = 33−66), both binding affinity and selectivity were significantly reduced by 3- to 5-fold, suggesting that the alkynyl linker might play a crucial but sensitive role for the titled system in providing the required hydrophobic interaction in the CB1 binding site. As well, it is noteworthy that compounds **25**−**27** remain behaving as neutral antagonists as with compounds **12**−**14**, but compounds **28**−**30** turn into partial agonists; again, these results demonstrated that in the series of alkynylthiophenes, a minor structural modification in the alkynyl side chain might contribute to the molecular switch in the intrinsic activity. By use of the optimum hex-1-ynyl linker as a fixed motif, compounds **31**−**33**, generated by the modification of the carboxamide N-substitution, were found to retain potent binding affinity ($IC_{50}$ = 2.1−3.0 nM) as with compounds **28**−**30**, indicating that the absence of the nitrogen adjacent to the carboxamide N might not affect the binding capability as highlighted by compound **28** ($IC_{50}$ = 1.4 nM) and its counterpart **33** ($IC_{50}$ = 2.1 nM). However, in sharp contrast to the high binding affinities observed, lower functional activities for compounds **31**−**33** ($EC_{50}$ = 29.8−74.0 nM) were obtained, suggesting that the additional nitrogen linked

**Scheme 4**[a]




**6** **42-48**

**42**: R = 4-phenylbut-1-ynyl
**43**: R = 3-methoxyprop-1-ynyl
**44**: R = 3-ethoxyprop-1-ynyl
**45**: R = 3-isopropoxyprop-1-ynyl
**46**: R = 3-(isopropylamino)prop-1-ynyl
**47**: R = 3-(dimethylamino)prop-1-ynyl
**48**: R = 3-phenoxy-prop-1-ynyl

[a] Reagents and conditions: (a) various alkynes, $Pd(PPh_3)_2Cl_2$, CuI, 2-ethanolamine, 60 °C, THF/$H_2O$ (1/1), 3 h, 92−95%.

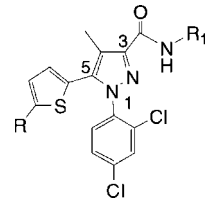
to the carboxamide N might play an important role in eliciting biological response of CB1 receptors during the induced-fit process. Also noted was the finding that the intrinsic property appears little influenced by the pattern of the carboxamide moiety as indicated by compounds **28**−**33**, wherein all behave as partial agonists irrespective of the nature of N-substitution. When the linear linker of compounds **25** and **26** were replaced with a global *tert*-butyl group, compounds **34** and **35** thus obtained only resulted in a slight improvement in biological activities ($IC_{50}$ = 21.7−32.7 nM; $EC_{50}$ = 28.9−158.4 nM), but their intrinsic property was found to switch from neutral antagonists to partial agonists, again demonstrating the versatile functionality of this new series. Along this line, a series of alkynylthiophenes appended with different cyclic rings in the alkynyl linker were also explored. As shown, five- and six-membered ring compounds **38**−**41** ($IC_{50}$ = 7.1−10.5 nM) were found to exhibit more potent CB1 binding affinity than cyclopropyl analogues **36** and **37** ($IC_{50}$ = 60.4 nM; 21.0 nM). This CB1 binding-capability trend is consistent with that of the corresponding linear-linker compounds as indicated below, *n*-hex-1-ynyl (e.g., **28**, **29**) > *n*-pent-1-ynyl (e.g., **12**, **13**) > *n*-but-1-ynyl (e.g., **25**, **26**), and is presumably attributed to the enhancement of receptor−ligand interactions as the ring size or the number of methylene unit in the linker increases. By this inference, an advanced compound **42** with an alkynyl linker containing an aromatic ring and a linear alkyl moiety was designed. As a result, both binding affinity and selectivity for **42** ($IC_{50}$ = 6.1 nM; $EC_{50}$ = 20.4 nM; CB2/1 = 285) toward CB1 receptors were significantly enhanced relative to the parent compound **25**. Taken together, the current SAR studies suggested that around the pyrazole 5-position of the rimonabant mimetics, a deep and flat crevice, constructed by a sequence of hydrophobic/aromatic residues as indicated by the proposed CB1-receptor homology model,[22a] might exist in the binding site to provide the required receptor−ligand interactions. Also noted is the finding that though some cyclic ring compounds, as demonstrated by **40** ($IC_{50}$ = 7.3 nM vs $EC_{50}$ = 442 nM) and **41** ($IC_{50}$ = 7.8 nM vs $EC_{50}$ = 293 nM), possess high binding affinity, their functional activities are extremely weak. Such a distinct difference between binding affinity and functional activity appears hard to be rationalized by current results and is worth further study to unveil the underlying cause.

On the other hand, to increase water solubility, compounds **43**−**48**, individually inserted with a heteroatom N or O in the linear alkynyl linker, were also prepared according to the synthetic Scheme 4. The assayed results for these compounds are displayed in Table 3. As shown, under such chemical modifications, compounds **12** and **25** were converted to compounds **43** and **44** with retained biological activity; however, when the linker is a branched alkyl chain as exemplified by **15** ($IC_{50}$ = 2.3 nM; $EC_{50}$ = 12.1 nM), the corresponding O-inserted **45** ($IC_{50}$ = 23.2 nM; $EC_{50}$ = 57.4 nM) and N-inserted **46** ($IC_{50}$ = 82.4 nM; $EC_{50}$ = 390.1 nM) resulted in a dramatic decrease in both binding affinity and functional activity. These results appear to indicate that the presence of the heteroatom in the alkynyl linker might somehow impair the receptor−ligand interactions. Similar observation for poorer biological activity was also made on N-inserted **47** ($IC_{50}$ = 124.2 nM; $EC_{50}$ = 348.8 nM) and O-inserted **48** ($IC_{50}$ = 43.0; $EC_{50}$ = 18.7 nM) compared to the parent compounds **15** and **42**, respectively, again reinforcing the evidence that the alkynyl linker is preferred to be a heteroatom-free hydrocarbon chain in order to maximize the hydrophobic interaction. Again, this finding lends further support to the previous proposal that CB1 binding site around the pyrazole-5 substitution might be a hydrophobic cavity made up of a sequence of hydrophobic/aromatic residues. Finally, representative compounds of the alkynylthiophene series, including **12** (NA), **14** (NA), **15** (PA), **16** (PA), **18** (IA), and **19** (IA), were selected for further CB1 binding affinity assay using radioligand [$^3$H]-**1**. It was found that in general, the observed $IC_{50}$ values, ranging from 1.2 to 4.5 nM, are significantly lower than those obtained using the standard radioligand (see Table 1), indicating that the binding mode of the titled series, particularly those behaving as NA or IA, bears high similarities to **1**.

Pharmacologically, many compounds in Tables 1 and 2 are qualified for in vivo efficacy studies in terms of potency and selectivity. Indeed, several have displayed promising effects on weight reduction and were selected for further development as antiobesity agents. Taking compound **18** as a representative example, a significant suppression of appetite in both the spontaneously feeding rat model (Figure 2) and DIO mouse model (Figure 3) was observed in a dose-dependent manner. It was found that though suppression of food intake for compound **18** was not as effective as the positive control **1**, appetite restoration with **18** appears to be much slower than **1** at a dose of 20 mg/kg after day 6 (Figure 3A). The similar restoration rate is also reflected in the body weight change studies in the long term DIO model. As depicted in Figure 3B, under treatment with compound **18** (20 mg/kg qd po) DIO mice resulted in reduction of body weight gradually and persistently throughout the 21-day period, achieving the same weight-loss efficacy as did compound **1** (10 mg/kg qd po) after day 14.

In summary, bioisosteric replacement of the conventional pyrazole-5 aryl group of rimonabant with a thiophene ring appended with an appropriate alkynyl unit proved to be viable, leading to a discovery of a new class of alkynylthiophenes with potent CB1 activity and excellent CB1/2 selectivity. Current SAR studies suggested that around the pyrazole 5-position, a deep and flat crevice surrounded by hydrophobic/aromatic residues might exist in the CB1 receptor binding site. Also encouraging was the unexpected finding that despite the existence of the pyrazole C3-carboxamide functionality, conventionally responsible for inverse agonism with many rimonabant-mimicking molecules, a minor structural modification in the novel alkynylthiophenes might be functionally adequate to induce a significant change of the intrinsic property. More importantly, in the long term DIO mouse studies, a significant effect on weight reduction was detected, thus pharmacologically validating the potential therapeutic utility of this series as antiobesity agents. Further efficacy studies, including central

**Table 2.** Biological Evaluation of 5-(5-Alkynylthiophen-2-yl)pyrazole Derivatives on hCB1 and hCB2 Receptors



| Compound | R | $R_1$ | $IC_{50}$ (nM)[a,c] hCB1 | $IC_{50}$ (nM)[a,c] hCB2 | $EC_{50}$ (nM)[b,c] | Selectivity CB2/CB1 | Intrinsic Property[d] |
|---|---|---|---|---|---|---|---|
| **25** | | | 65.4 ± 32.2 | 4328.3 ± 1016.2 | 51.4 ± 18.5 | 66 | NA |
| **26** | | | 28.3 ± 9.9 | 921.0 ± 224.5 | 35.5 ± 6.5 | 33 | NA |
| **27** | | | 24.2 ± 1.2 | 1057.8 ± 79.7 | 36.4 ± 11.2 | 44 | NA |
| **28** | | | 1.4 ± 0.4 | 310.5 ± 34.0 | 7.9 ± 0.1 | 222 | PA |
| **29** | | | 1.3 ± 0.1 | 158.0 ± 30.2 | 5.7 ± 0.4 | 122 | PA |
| **30** | | | 1.7 ± 0.3 | 564.0 ± 154.1 | 4.8 ± 1.1 | 332 | PA |
| **31** | | | 3.0 ± 0.2 | 637.7 ± 117.2 | 29.8 ± 7.5 | 213 | PA |
| **32** | | | 2.6 ± 0.7 | 260.6 ± 96.6 | 74.0 ± 6.9 | 100 | PA |
| **33** | | | 2.1 ± 0.2 | 278.3 ± 32.4 | 43.9 ± 9.9 | 133 | PA |
| **34** | $^t$Bu | | 32.7 ± 3.6 | 1900.1 ± 406.4 | 28.9 ± 5.2 | 59 | PA |
| **35** | $^t$Bu | | 21.7 ± 7.4 | 1158.1 ± 373.7 | 158.4 ± 63.6 | 53 | PA |
| **36** | | | 60.4 ± 21.6 | 4234.4 ± 225.5 | 72.9 ± 24.1 | 70 | NA |
| **37** | | | 21.0 ± 5.4 | 5719.5 ± 717.7 | 104.8 ± 22.9 | 272 | NA |
| **38** | | | 7.1 ± 1.7 | 1809.1 ± 29.4 | 24.5 ± 4.2 | 255 | PA |
| **39** | | | 10.5 ± 1.2 | 901.7 ± 200.3 | 99.3 ± 18.8 | 86 | PA |
| **40** | | | 7.3 ± 4.6 | 1576.4 ± 241.6 | 442.4 ± 40.9 | 216 | PA |
| **41** | | | 7.8 ± 0.1 | 1725.9 ± 61.7 | 293.6 ± 152.4 | 221 | PA |
| **42** | | | 6.1 ± 0.4 | 1749.8 ± 245.0 | 20.4 ± 9.8 | 285 | PA |
| | **Compound 1** | | 15.0 ± 1.8 | 1939.8 ± 131.1 | 18.2 ± 9.5 | 129 | IA |

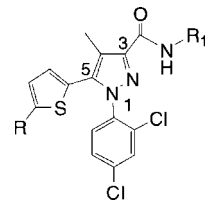
[a] Binding affinity determined by inhibition of [$^3$H]-CP55940 ([$^3$H]-**49**) binding to hCB1- or hCB2-transfected HEK 293 membrane is expressed as $IC_{50}$. [b] Functional activity determined by inhibition of Eu-GTP binding to hCB1-transfected HEK 293 membrane is expressed as $EC_{50}$. [c] Data are expressed as the mean ± SD of at least three independent experiments. [d] According to the definition reported in the literature,[36] the intrinsic property of each compounds is identified as an IA, NA, or PA as assessed by the Eu-GTP biding to hCB1-transfected HEK 293 membrane (see Figure 4).

nervous system toxicities and behavioral effects,[33] are under active investigation and results will be reported elsewhere in due course.

## Experimental Section

**A. Chemistry.** Unless otherwise stated, all materials used were commercially available and used as supplied. Reactions requiring anhydrous conditions were performed in flame-dried glassware, and cooled under an argon or nitrogen atmosphere. Unless otherwise stated, reactions were carried out under argon or nitrogen and monitored by analytical thin layer chromatography performed on glass-backed plates (5 cm × 10 cm) precoated with silica silica gel 60 $F_{254}$ as supplied by Merck. Visualization of the resulting chromatograms was done by looking under an ultraviolet lamp ($\lambda$ = 254 nm) followed by dipping in an ethanol solution of vanillin (5% w/v) containing sulfuric acid (3% v/v) or phosphomolybdic acid (2.5% w/v) and charring by heat gun. Solvents for reactions were dried and distilled under an argon or nitrogen atmosphere prior to use as follows: THF, diethyl ether (ether), and DMF from a dark-blue solution of sodium benzophenone ketyl; toluene, dichromethane, and pyridine from calcium hydride. Flash chromatography was used routinely for purification and separation of product mixtures using silica gel 60 of 230−400 mesh size as supplied by Merck. Eluent systems are given in volume/volume concentrations. Combustion elemental analyses were performed by

**Table 3.** Biological Evaluation of 5-(5-Heteroalkynylthiophen-2-yl)pyrazole Derivatives on hCB1 and hCB2 Receptors



| Compound | R | $R_1$ | $IC_{50}$ (nM)[a,c] hCB1 | $IC_{50}$ (nM)[a,c] hCB2 | $EC_{50}$ (nM)[b,c] | Selectivity CB2/CB1 | Intrinsic Property[d] |
|---|---|---|---|---|---|---|---|
| **43** | MeO | | 65.3 ± 11.0 | 2737.4 ± 296.1 | 142.7 ± 16.2 | 42 | ND[e] |
| **44** | EtO | | 12.7 ± 2.8 | 985.6 ± 302.9 | 25.5 ± 2.5 | 78 | IA |
| **45** | $^{i}$PrO | | 23.2 ± 6.5 | 1761.1 ± 219.3 | 57.4 ± 29.8 | 76 | PA |
| **46** | $^{i}$PrN | | 82.4 ± 20.1 | 7179.1 ± 1183.7 | 390.1 ± 83.5 | 87 | ND[e] |
| **47** | $Me_2N$ | | 124.2 ± 39.5 | 1269.4 ± 482.0 | 348.8 ± 54.2 | 10 | ND[e] |
| **48** | PhO | | 43.0 ± 11.3 | 7032.2 ± 704.0 | 18.7 ± 4.4 | 164 | NA |
| | **Compound 1** | | 15.0 ± 1.8 | 1939.8 ± 131.1 | 18.2 ± 9.5 | 129 | IA |

[a] Binding affinity determined by inhibition of [$^3$H]-CP55940 ([$^3$H]-**49**) binding to hCB1- or hCB2-transfected HEK 293 membrane is expressed as $IC_{50}$. [b] Functional activity determined by inhibition of Eu-GTP binding to hCB1-transfected HEK 293 membrane is expressed as $EC_{50}$. [c] Data are expressed as the mean ± SD of at least three independent experiments. [d] According to the definition reported in the literature,[36] the intrinsic property of each compounds is identified as an IA, NA, or PA as assessed by the Eu-GTP biding to hCB1-transfected HEK 293 membrane (see Figure 4). [e] ND: not determined.

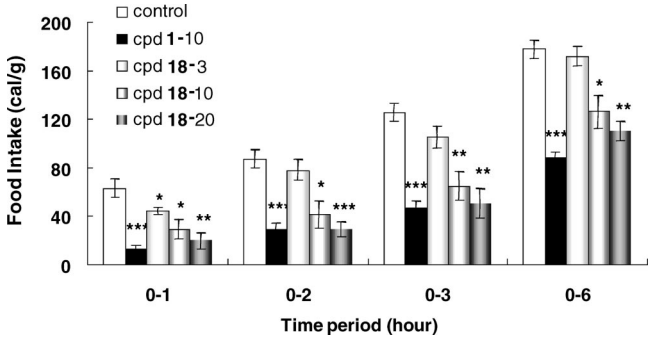



**Figure 2.** Cumulative food intake of compound **18** at an oral dose of 3 mg/kg (cpd **18**-3) ($n = 6$), 10 mg/kg (cpd **18**-10) ($n = 4$), and 20 mg/kg (cpd **18**-20) ($n = 5$) was examined in rat spontaneous feeding model compared to that of **1** at an oral dose of 10 mg/kg (cpd **1**-10) ($n = 5$) and vehicle only ($n = 5$). Data are presented as mean ± standard error: (***) $P < 0.001$; (**) $P < 0.005$; (*) $P < 0.05$. The experimental protocol is detailed in section B4.

the microanalytical laboratory at National Chiao Tung University, Taiwan, ROC. $^1$H NMR and $^{13}$C NMR spectra were recorded on Varian Mercury-300 (300 MHz) or Varian Mercury-400 (400 MHz). Chloroform-*d* or dimethyl sulfoxide-$d_6$ was used as the solvent and TMS ($\delta$ 0.00 ppm) as an internal standard. Chemical shift values are reported in ppm relative to the TMS in delta ($\delta$) units. Multiplicities are recorded as s (singlet), brs (broad singlet), d (doublet), t (triplet), q (quartet), dd (doublet of doublet), dt (doublet of triplet), m (multiplet). Coupling constants ($J$) are expressed in Hz. Electrospray mass spectra (ESMS) were recorded using an agilent 1100 MSD mass spectrometer. Spectral data were recorded as *m*/*z* values.

**Lithium Salt of Ethyl 3-Methyl-2,4-dioxo-4-thiophen-2-ylbutanonate (2).** To a magnetically stirred solution of lithium bis(trimethylsilyl)amide (22.2 mL, 22.20 mmol, 1.0 M in THF) in diethyl ether (40 mL) at −78 °C was added 1-(2-thienyl)-1-propanone (2.81 g, 20.04 mmol) in diethyl ether (15 mL) dropwise under an argon atmosphere. After the mixture was stirred at the same temperature for an additional 45 min, diethyl oxalate (3.3 mL, 24.40 mmol) was added dropwise. The reaction mixture was allowed to warm to room temperature and stirred for another 16 h. The reaction precipitate was filtered, washed with diethyl ether, and dried under vacuum to afford the crude lithium salt **2** (4.21 g, 85%) as a pale-yellow solid.

**1-(2,4-Dichlorophenyl)-4-methyl-5-thiophen-2-yl-1*H*-pyrazole-3-carboxylic Acid Ethyl Ester (3).** To a solution of lithium salt **2** (3.21 g, 13.04 mmol) in ethanol (35 mL) was added 2,4-dichlorophenylhydrazine hydrochloride (3.01 g, 14.05 mmol) in one portion at room temperature under nitrogen. The resulting mixture was stirred at the same temperature for 20 h. After reaction was complete, the precipitate was filtered, washed with ethanol and diethyl ether, and dried under vacuum to give a light-yellow solid (3.31 g). This crude solid, without purification, was dissolved in acetic acid (30 mL) and heated to reflux for 24 h. The reaction mixture was poured into ice−water and extracted with ethyl acetate (2 × 30 mL). The combined extracts were washed with water, saturated aqueous sodium bicarbonate, and brine, dried over anhydrous sodium sulfate, filtered, and evaporated. Purification by flash column chromatography on silica gel with *n*-hexane/ethyl acetate (9:1) gave ester **3** (2.49 g, 50% over two steps) as a white solid: mp 121−122 °C; $^1$H NMR ($CDCl_3$) $\delta$ 7.43 (d, $J = 2.1$ Hz, 1H), 7.39−7.34 (m, 2H), 7.32 (d, $J = 3.6$ Hz, 1H), 7.00 (dd, $J = 5.1$, 3.6 Hz, 1H), 6.89 (d, $J = 5.1$ Hz, 1H), 4.45 (q, $J = 7.2$ Hz, 2H), 2.44 (s, 3H), 1.42 (t, $J = 7.2$ Hz, 3H); $^{13}$C NMR ($CDCl_3$) $\delta$ 162.7, 142.8, 137.8, 136.3, 136.0, 133.9, 131.0, 129.6, 128.8, 128.5, 127.7, 127.6, 127.2, 119.9, 60.9, 14.4, 9.9. ESMS *m*/*z*: 381.0 (M + 1), 403.0 (M + 23).

**5-(5-Bromothiophen-2-yl)-1-(2,4-dichlorophenyl)-4-methyl-1*H*-pyrazole-3-carboxylic Acid Ethyl Ester (4).** To a magnetically stirred solution of **3** (2.21 g, 5.79 mmol) in acetonitrile (20 mL) was added NBS (1.24 g, 6.96 mmol) in small portions under argon at 0 °C. The resulting mixture was then warmed to room temperature and stirred for 16 h. The reaction was quenched with

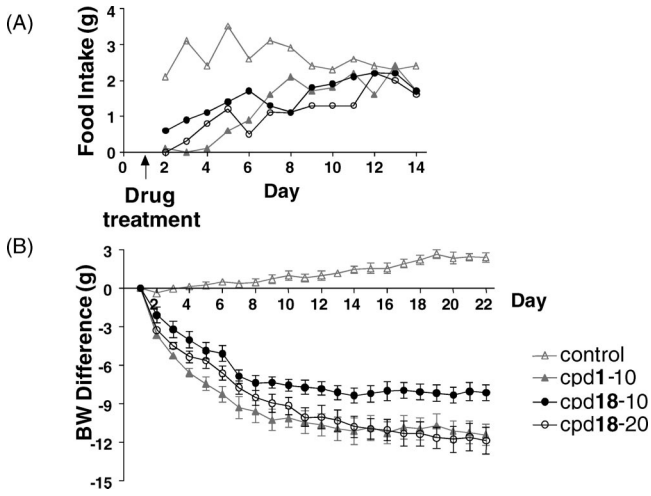



**Figure 3.** Long-term in vivo efficacy of compound **18** at an oral dose of 10 mg/kg (cpd **18**-10) and 20 mg/kg (cpd **18**-20) compared to compound **1** at an oral dose of 10 mg/kg (cpd **1**-10) in DIO mouse model ($n = 6$ for every treatment group): (A) 24 h food intake of the first 14 days after drug treatment; (B) body weight (BW) difference during the 21-day treatment. The experimental protocol is detailed in section B5.

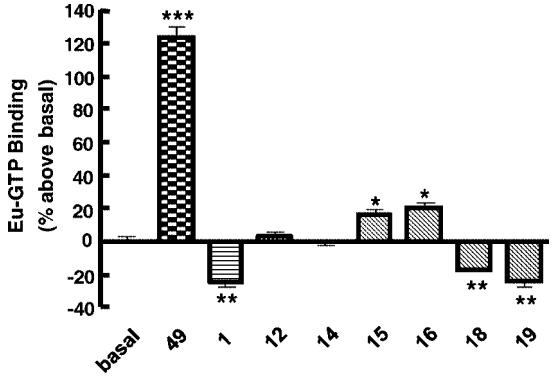



**Figure 4.** Eu-GTP binding assay of alkynylthiophene **12**, **14**−**16**, **18**, and **19**, compounds **1** and **49** (see footnote a in Table 1) at a concentration of 10 $\mu$M on the hCB1 cannabinoid receptor was conducted. Data are expressed as the mean ± SD of at least three experiments performed in duplicate. Statistical significance was assessed by unpaired two-tailed *t*-test using the GraphPad Prism program (GraphPad Software, San Diego, CA). $P < 0.05$ (∗) was considered significant. Compounds **12** and **14** with the induced Eu-GTP binding intensity around the basal level are defined as NA. Compounds **15** and **16** with a significant increase in the intensity relative to the basal level are defined as PA. Compounds **18** and **19** with a significant decrease in the binding intensity are defined as IA.

saturated aqueous sodium thiosulfate and concentrated under reduced pressure to remove acetonitrile. The aqueous layer was extracted with ethyl acetate (2 × 40 mL). The organic layers were combined, washed with water, brine, dried over anhydrous sodium sulfate, and concentrated to give the crude residue, which was subjected to purification by flash chromatography on silica gel with *n*-hexane/ethyl acetate (9:1) to afford bromo ester **4** (2.53 g, 95%) as a white solid: mp 93−94 °C; $^1$H NMR ($CDCl_3$) $\delta$ 7.46 (d, $J =$ 1.8 Hz, 1H), 7.36−7.35 (m, 1H), 7.34 (d, $J = 1.8$ Hz, 1H), 6.96 (d, $J = 3.9$ Hz, 1H), 6.64 (d, $J = 3.9$ Hz, 1H), 4.44 (q, $J = 7.2$ Hz, 2H), 2.42 (s, 3H), 1.42 (t, $J = 7.2$ Hz, 3H); $^{13}$C NMR ($CDCl_3$) $\delta$ 161.7, 142.2, 136.1, 135.8, 134.9, 133.0, 130.3, 129.5, 129.3, 128.6, 127.2, 119.5, 114.2, 114.1, 60.2, 13.8, 9.3. ESMS *m*/*z*: 460.9 (M + 1), 482.9 (M + 23). Anal. ($C_{17}H_{13}BrCl_2N_2O_2S$) C, H, N.

**5-(5-Bromothiophen-2-yl)-1-(2,4-dichlorophenyl)-4-methyl-1*H*-pyrazole-3-carboxylic Acid (5).** To a solution of bromo ester **4** (2.00 g, 4.35 mmol) in methanol (20 mL) was added potassium hydroxide (0.51 g, 9.09 mmol) in methanol (7 mL) dropwise at room temperature. The resulting mixture was heated to reflux for 3 h. After hydrolysis was complete, the reaction mixture was cooled to room temperature, poured into ice−water, and acidified with 10% hydrochloric acid. The precipitate was filtered, washed with water, and dried under vacuum to give thiophene carboxylic acid **5** (1.81 g, 96%) as a white solid: mp 214.5−215 °C; $^1$H NMR ($CDCl_3$) $\delta$ 7.49 (s, 1H), 7.40−7.30 (m, 2H), 6.97 (d, $J = 3.6$ Hz, 1H), 6.66 (d, $J = 3.6$ Hz, 1H), 2.48 (s, 3H); $^{13}$C NMR ($CDCl_3$) $\delta$ 165.3, 142.1, 137.4, 136.8, 135.4, 133.6, 130.7, 130.3, 130.2, 129.7, 129.4, 127.9, 120.8, 115.2, 9.8. ESMS *m*/*z*: 432.9 (M + 1). Anal. ($C_{15}H_9BrCl_2N_2O_2S$) C, H, N.

**5-(5-Bromothiophen-2-yl)-1-(2,4-dichlorophenyl)-4-methyl-*N*-(piperidin-1-yl)-1*H*-pyrazole-3-carboxamide (6).** To a solution of thiophene carboxylic acid **5** (87 mg, 0.20 mmol) in dichloromethane (4 mL) at 0 °C were added triethylamine (84 $\mu$L, 0.60 mmol) and trimethylacetyl chloride (48 $\mu$L, 0.40 mmol). The mixture was allowed to warm to room temperature and stirred for 2 h to form carboxylic anhydride, which in turn was transferred slowly to a mixture of 1-aminopiperidine (44 $\mu$L, 0.40 mmol) and triethylamine (84 $\mu$L, 0.60 mmol) in dichloromethane (4 mL) at 0 °C. After the mixture was warmed and stirred at room temperature for 2 h, the reaction was quenched with water. The aqueous solution was separated and extracted with dichloromethane (2 × 10 mL). The combined extracts were washed with brine, dried over anhydrous sodium sulfate, filtered, and evaporated. Purification of the crude residue by flash chromatography on silica gel eluting with *n*-hexane/ethyl acetate (5:1) gave rise to carboxamide **6** (73 mg, 71% over two steps) as a white solid: mp 98−100 °C; $^1$H NMR ($CDCl_3$) $\delta$ 7.65 (s, 1H), 7.50 (s, 1H), 7.40−7.28 (m, 2H), 6.95 (d, $J = 3.6$ Hz, 1H), 6.63 (d, $J = 3.6$ Hz, 1H), 2.85−2.78 (m, 4H), 2.45 (s, 3H), 1.80−1.70 (m, 4H), 1.50−1.40 (m, 2H); $^{13}$C NMR ($CDCl_3$) $\delta$ 159.5, 144.2, 136.8, 136.4, 135.5, 133.5, 130.6, 130.2, 130.1, 130.0, 128.9, 127.9, 119.2, 114.7, 56.9, 25.3, 23.2, 9.5. ESMS *m*/*z*: 515.2 (M + 1). Anal. ($C_{20}H_{19}BrCl_2N_4OS$) Calcd: C 46.71; H 3.72; N 10.89. Found: C 46.75; H 4.23; N 10.41.

***N*-(Azepan-1-yl)-5-(5-bromothiophen-2-yl)-1-(2,4-dichlorophenyl)-4-methyl-1*H*-pyrazole-3-carboxamide (7).** Carboxamide **7** was synthesized following a similar coupling-reaction procedure as described above for **6**. Thiophene carboxylic acid **5** (87 mg, 0.20 mmol) was treated with triethylamine (84 $\mu$L, 0.60 mmol) and trimethylacetyl chloride (48 $\mu$L, 0.40 mmol) in dichloromethane (4 mL). The crude carboxylic anhydride thus formed reacted with azepan-1-amine (49 $\mu$L, 0.40 mmol) and triethylamine (84 $\mu$L, 0.60 mmol) in dichloromethane (4 mL) to give compound **7** (86 mg, 65% over two steps) as a white solid: mp 145−146 °C; $^1$H NMR ($CDCl_3$) $\delta$ 8.06 (s, 1H), 7.49 (d, $J = 2.0$ Hz, 1H), 7.40−7.28 (m, 2H), 6.95 (d, $J = 3.6$ Hz, 1H), 6.63 (d, $J = 3.6$ Hz, 1H), 3.20−3.10 (m, 4H), 2.45 (s, 3H), 1.80−1.60 (m, 8H); $^{13}$C NMR ($CDCl_3$) $\delta$ 159.9, 144.2, 136.8, 136.4, 135.5, 133.6, 130.6, 130.2, 130.1, 130.0, 128.9, 127.9, 119.1, 114.7, 58.2, 26.8, 26.2, 9.5. ESMS *m*/*z*: 529.3 (M + 1). Anal. ($C_{21}H_{21}BrCl_2N_4OS$) C, H, N.

**5-(5-Chlorothiophen-2-yl)-1-(2,4-dichlorophenyl)-4-methyl-*N*-(piperidin-1-yl)-1*H*-pyrazole-3-carboxamide (8).** Compound **8** was prepared following a similar synthetic procedure as described for compound **6** in Scheme 1, with the exception that 1-(2-thienyl)-1-propanone was replaced with 1-(5-chlorothiophen-2-yl)propan-1-one as the starting material. Carboxamide **8** (131 mg) was obtained as a white solid after purification: mp 89−91 °C; $^1$H NMR ($CDCl_3$) $\delta$ 7.57 (s, 1H), 7.40 (s, 1H), 7.30−7.28 (m, 2H), 6.72 (d, $J = 3.6$ Hz, 1H), 6.57 (d, $J = 3.6$ Hz, 1H), 2.80−2.70 (m, 4H), 2.36 (s, 3H), 1.70−1.60 (m, 4H), 1.40−1.28 (m, 2H); $^{13}$C NMR ($CDCl_3$) $\delta$ 159.4, 144.1, 136.7, 136.3, 135.4, 133.4, 132.2, 130.6, 130.0, 128.0, 127.8, 127.1, 126.2, 119.1, 56.8, 25.2, 23.1, 9.3. ESMS *m*/*z*: 469.0 (M + 1).

***N*-(Azepan-1-yl)-5-(5-chlorothiophen-2-yl)-1-(2,4-dichlorophenyl)-4-methyl-1*H*-pyrazole-3-carboxamide (9).** Compound **9** was synthesized with a similar coupling-reaction procedure as described above for compound **8**. Chlorothiophene carboxylic acid (166 mg, 0.43 mmol) was treated with triethylamine (180 $\mu$L, 1.29 mmol) and trimethylacetyl chloride (104 $\mu$L, 0.86 mmol) in dichlo-

romethane (4 mL). The crude carboxylic anhydride thus formed reacted with azepan-1-amine (105 μL, 0.86 mmol) and triethylamine (180 μL, 1.29 mmol) in dichloromethane (4 mL) to give carboxamide **9** (134 mg, 65% over two steps) as a white solid: mp 124.5−125.5 °C; $^1$H NMR ($CDCl_3$) $\delta$ 7.99 (s, 1H), 7.49 (s, 1H), 7.30−7.28 (m, 2H), 6.73 (d, $J$ = 4.0 Hz, 1H), 6.58 (d, $J$ = 4.0 Hz, 1H), 3.10−3.00 (m, 4H), 2.37 (s, 3H), 1.70−1.50 (m, 8H); $^{13}$C NMR ($CDCl_3$) $\delta$ 159.9, 144.2, 136.8, 136.4, 135.5, 133.6, 132.3, 130.7, 130.2, 128.0, 127.9, 127.2, 126.3, 119.2, 58.2, 26.8, 26.2, 9.5. ESMS *m*/*z*: 483.0 (M + 1).

**5-(5-Pentynylthiophen-2-yl)-1-(2,4-dichlorophenyl)-4-methyl-1*H*-pyrazole-3-carboxylic Acid Ethyl Ester (10).** To a mixture of ester **4** (0.93 g, 2.02 mmol), $PdCl_2(PPh_3)_2$ (70 mg, 0.10 mmol), and CuI (12 mg, 0.06 mmol) in THF (12 mL) was added 1-pentyne (0.41 mL, 4.04 mmol) and 0.5 M aqueous solution of 2-ethanolamine (12 mL). The resulting mixture was heated at 60 °C for 6 h. After cooling to room temperature, the reaction mixture was poured into water (20 mL) and the aqueous solution was separated and extracted with diethyl ether (2 × 20 mL). The combined organic layers were washed with water, brine, dried over anhydrous sodium sulfate, and concentrated under reduced pressure to give crude residue, which was subjected to purification by flash column chromatography on silica gel with *n*-hexane/ethyl acetate (15:1) to afford the desired product **10** (0.84 g, 94%) as a white solid: mp 91−91.5 °C; $^1$H NMR ($CDCl_3$) $\delta$ 7.45 (d, $J$ = 1.6 Hz, 1H), 7.41−7.26 (m, 2H), 6.97 (d, $J$ = 3.6 Hz, 1H), 6.72 (d, $J$ = 3.6 Hz, 1H), 4.43 (q, $J$ = 7.2 Hz, 2H), 2.45 (s, 3H), 2.36 (t, $J$ = 7.2 Hz, 2H), 1.58 (sextet, $J$ = 7.2 Hz, 2H), 1.40 (t, $J$ = 7.2 Hz, 3H), 1.00 (t, $J$ = 7.2 Hz, 3H); $^{13}$C NMR ($CDCl_3$) $\delta$ 162.2, 142.6, 136.9, 136.1, 135.5, 133.4, 130.7, 130.7, 129.7, 128.1, 128.0, 127.5, 126.4, 119.8, 96.3, 72.8, 60.6, 21.6, 21.3, 14.1, 13.3, 9.7. ESMS *m*/*z*: 447.2 (M + 1).

**1-(2,4-Dichlorophenyl)-4-methyl-5-(5-(4-methylpent-1-ynyl)thiophen-2-yl)-1*H*-pyrazole-3-carboxylic Acid Ethyl Ester (10a).** Compound **10a** was synthesized with a similar coupling-reaction procedure as described for **10**. Treatment of ester **4** (0.92 g, 2.00 mmol) with $PdCl_2(PPh_3)_2$ (77 mg, 0.11 mmol), CuI (14 mg, 0.07 mmol), 4-methylpent-1-yne (0.34 g, 4.16 mmol), and 2-ethanolamine (0.5 M, 12 mL) in THF (12 mL) gave compound **10a** (0.85 g, 92%) as a white solid: mp 112−113 °C; $^1$H NMR ($CDCl_3$) $\delta$ 7.33 (d, $J$ = 2.0 Hz, 1H), 7.28 (d, $J$ = 8.0 Hz, 1H), 6.98 (dd, $J$ = 8.0, 2.0 Hz, 1H), 6.86 (d, $J$ = 3.6 Hz, 1H), 6.60 (d, $J$ = 3.6 Hz, 1H), 4.31 (q, $J$ = 6.8 Hz, 2H), 2.33 (s, 3H), 2.16 (d, $J$ = 6.8 Hz, 2H), 1.75 (septet, $J$ = 6.8 Hz, 1H), 1.28 (t, $J$ = 6.8 Hz, 3H), 0.88 (d, $J$ = 6.8 Hz, 6H); $^{13}$C NMR ($CDCl_3$) $\delta$ 162.1, 142.5, 136.8, 136.0, 135.4, 133.4, 130.6, 130.5, 129.6, 128.0, 127.9, 127.5, 126.4, 119.7, 95.4, 73.4, 60.5, 28.4, 27.6, 21.6, 14.0, 9.6. ESMS *m*/*z*: 461.0 (M + 1).

**1-(2,4-Dichlorophenyl)-4-methyl-5-[((*E*)-5-pent-1-enyl)-thiophen-2-yl]-1*H*-pyrazole-3-carboxylic Acid Ethyl Ester (10b).** A mixture of ester **4** (0.46 g, 1.00 mmol), (*E*)-pent-1-enylboronic acid (137 mg, 1.20 mmol), tetrakis(triphenylphosphine)palladium (116 mg, 0.10 mmol), and cesium carbonate (0.66 g, 2.02 mmol) in DME (10 mL) was heated to reflux for 3 h. After the reaction was complete, the precipitate was filtered and solvent was evaporated under reduced pressure. The residue thus obtained was further purified by flash chromatography with *n*-hexane/ethyl acetate (9:1) to give compound **10b** (0.34 g, 75%) as a white solid: mp 91−91.5 °C; $^1$H NMR ($CDCl_3$) $\delta$ 7.44 (d, $J$ = 1.8 Hz, 1H), 7.36 (s, 1H), 7.32 (d, $J$ = 1.8 Hz, 1H), 6.72 (d, $J$ = 3.3 Hz, 1H), 6.66 (d, $J$ = 3.3 Hz, 1H), 6.38 (d, $J$ = 15.9 Hz, 1H), 6.02 (dt, $J$ = 15.9, 7.2 Hz, 1H), 4.44 (q, $J$ = 7.2 Hz, 2H), 2.45 (s, 3H), 2.16−2.08 (m, 2H), 1.44 (sextet, $J$ = 7.2 Hz, 2H), 1.41 (t, $J$ = 7.2 Hz, 3H), 0.92 (t, $J$ = 7.2 Hz, 3H); $^{13}$C NMR ($CDCl_3$) $\delta$ 162.5, 145.4, 142.7, 137.8, 136.0, 135.9, 133.6, 132.4, 130.8, 129.8, 128.9, 127.6, 125.5, 124.0, 122.4, 119.7, 60.8, 34.7, 22.1, 14.3, 13.5, 9.9. ESMS *m*/*z*: 449.3 (M + 1).

**5-(5-(But-1-ynyl)thiophen-2-yl)-1-(2,4-dichlorophenyl)-4-methyl-1*H*-pyrazole-3-carboxylic Acid Ethyl Ester (10c).** According to the coupling-reaction procedure applied to **10**, compound **10c** was obtained as a pale-yellow oil (0.80 g, 92%). $^1$H NMR ($CDCl_3$) $\delta$ 7.44 (d, $J$ = 2.4 Hz, 1H), 7.39 (d, $J$ = 8.4 Hz, 1H), 7.32 (dd, $J$ = 8.4, 2.4 Hz, 1H), 6.97 (d, $J$ = 4.0 Hz, 1H), 6.72 (d, $J$ = 4.0 Hz, 1H), 4.43 (q, $J$ = 7.2 Hz, 2H), 2.44 (s, 3H), 2.39 (q, $J$ = 7.2 Hz, 2H), 1.40 (t, $J$ = 7.2 Hz, 3H), 1.18 (t, $J$ = 7.2 Hz, 3H); $^{13}$C NMR ($CDCl_3$) $\delta$ 162.2, 142.5, 136.9, 136.1, 135.5, 133.4, 130.7, 130.6, 129.7, 128.1, 128.0, 127.5, 126.4, 119.8, 97.6, 71.9, 60.6, 14.1, 13.2, 13.0, 9.7. ESMS *m*/*z*: 433.1 (M + 1).

**1-(2,4-Dichlorophenyl)-5-(5-(hex-1-ynyl)thiophen-2-yl)-4-methyl-1*H*-pyrazole-3-carboxylic Acid Ethyl Ester (10d).** According to the coupling-reaction procedure applied to **10**, compound **10d** was obtained as a white solid (0.86 g, 96%): mp 73−74 °C; $^1$H NMR ($CDCl_3$) $\delta$ 7.44 (s, 1H), 7.40−7.24 (m, 2H), 6.96 (d, $J$ = 3.6 Hz, 1H), 6.69 (d, $J$ = 3.6 Hz, 1H), 4.31 (q, $J$ = 7.2 Hz, 2H), 2.33 (s, 3H), 2.39 (t, $J$ = 7.2 Hz, 2H), 1.50−1.33 (m, 4H), 1.28 (t, $J$ = 7.2 Hz, 3H), 0.91 (t, $J$ = 7.2 Hz, 3H); $^{13}$C NMR ($CDCl_3$) $\delta$ 162.1, 142.5, 136.8, 136.0, 135.5, 133.4, 130.6, 130.5, 129.6, 128.0, 127.9, 127.4, 126.4, 119.7, 96.4, 72.5, 60.5, 30.1, 21.6, 19.0, 14.0, 13.2, 9.6. ESMS *m*/*z*: 461.1 (M + 1).

**1-(2,4-Dichlorophenyl)-5-(5-(3,3-dimethylbut-1-ynyl)thiophen-2-yl)-4-methyl-1*H*-pyrazole-3-carboxylic Acid Ethyl Ester (10e).** According to the coupling-reaction procedure applied to **10**, compound **10e** was obtained as a white solid (0.87 g, 94%): mp 133−134 °C; $^1$H NMR ($CDCl_3$) $\delta$ 7.44 (d, $J$ = 1.8 Hz, 1H), 7.40−7.28 (m, 2H), 6.96 (d, $J$ = 3.6 Hz, 1H), 6.67 (d, $J$ = 3.6 Hz, 1H), 4.40 (q, $J$ = 7.2 Hz, 2H), 2.42 (s, 3H), 1.41 (t, $J$ = 7.2 Hz, 3H), 1.28 (s, 9H); $^{13}$C NMR ($CDCl_3$) $\delta$ 162.5, 142.8, 137.2, 136.3, 135.7, 133.7,130.9, 130.8, 130.0, 128.4, 128.2, 127.7, 126.6, 120.1, 104.3, 71.4, 60.9, 30.6, 28.2, 14.3, 9.8. ESMS *m*/*z*: 461.0 (M + 1).

**5-(5-(Cyclopropylethynyl)thiophen-2-yl)-1-(2,4-dichlorophenyl)-4-methyl-1*H*-pyrazole-3-carboxylic Acid Ethyl Ester (10f).** According to the coupling-reaction procedure applied to **10**, compound **10f** was obtained as a pale-yellow oil (0.85 g, 96%). $^1$H NMR ($CDCl_3$) $\delta$ 7.48 (d, $J$ = 1.5 Hz, 1H), 7.40−7.26 (m, 2H), 6.96 (d, $J$ = 3.6 Hz, 1H), 6.70 (d, $J$ = 3.6 Hz, 1H), 4.44 (q, $J$ = 6.9 Hz, 2H), 2.43 (s, 3H), 1.50−1.38 (m, 1H), 1.41 (t, $J$ = 6.9 Hz, 3H), 0.98−0.78 (m, 4H); $^{13}$C NMR ($CDCl_3$) $\delta$ 162.4, 142.8, 137.1, 136.3, 135.7, 133.7, 131.0, 130.8, 129.9, 128.3, 127.7, 126.6, 120.0, 99.6, 67.9, 60.8, 14.3, 9.8, 8.7, 0.2. ESMS *m*/*z*: 445.2 (M + 1).

**5-(5-(Cyclopentylethynyl)thiophen-2-yl)-1-(2,4-dichlorophenyl)-4-methyl-1*H*-pyrazole-3-carboxylic Acid Ethyl Ester (10g).** According to the coupling-reaction procedure applied to **10**, compound **10g** was obtained as a white solid (0.90 g, 95%): mp 62−63.5 °C; $^1$H NMR ($CDCl_3$) $\delta$ 7.45 (d, $J$ = 2.1 Hz, 1H), 7.40−7.27 (m, 2H), 6.96 (d, $J$ = 3.6 Hz, 1H), 6.69 (d, $J$ = 3.6 Hz, 1H), 4.44 (q, $J$ = 7.2 Hz, 2H), 2.90−2.70 (m, 1H), 2.43 (s, 3H), 2.08−1.45 (m, 8H), 1.40 (t, $J$ = 7.2 Hz, 3H); $^{13}$C NMR ($CDCl_3$) $\delta$ 161.7, 142.2, 136.6, 135.7, 135.2, 133.1, 130.4, 130.2, 129.3, 127.8, 127.6, 127.2, 126.2, 119.4, 100.2, 71.9, 60.2, 33.0, 30.3, 24.5, 13.8, 9.3. ESMS *m*/*z*: 473.1 (M + 1).

**5-(5-(Cyclohexylethynyl)thiophen-2-yl)-1-(2,4-dichlorophenyl)-4-methyl-1*H*-pyrazole-3-carboxylic Acid Ethyl Ester (10h).** According to the coupling-reaction procedure applied to **10**, compound **10h** was obtained as a white solid (0.90 g, 93%): mp 61.5−62 °C; $^1$H NMR ($CDCl_3$) $\delta$ 7.45 (d, $J$ = 1.5 Hz, 1H), 7.40−7.28 (m, 2H), 6.97 (d, $J$ = 3.6 Hz, 1H), 6.69 (d, $J$ = 3.6 Hz, 1H), 4.44 (q, $J$ = 6.9 Hz, 2H), 2.64−2.51 (m, 1H), 2.44 (s, 3H), 1.90−1.64 (m, 4H), 1.41 (t, $J$ = 6.9 Hz, 3H), 1.60−1.20 (m, 6H); $^{13}$C NMR ($CDCl_3$) $\delta$ 162.5, 142.8, 137.2, 136.3, 135.8, 133.7, 130.9, 130.8, 130.0, 128.4, 128.2, 127.7, 126.8, 120.1, 100.5, 72.7, 60.9, 32.3, 29.9, 25.7, 24.8, 14.3, 9.9. ESMS *m*/*z*: 487.3 (M + 1).

**1-(2,4-Dichlorophenyl)-4-methyl-5-(5-(pent-1-ynyl)thiophen-2-yl)-1*H*-pyrazole-3-carboxylic Acid (11).** To a magnetically stirred solution of ester **10** (0.92 g, 2.05 mmol) in methanol (5 mL) was added potassium hydroxide (0.25 g, 4.46 mmol) in methanol (5 mL) dropwise at room temperature. The reaction mixture was heated to reflux for 3 h. After hydrolysis was complete, the reaction mixture was cooled to room temperature, poured into ice−water, and acidified with 10% hydrochloric acid. The precipitate was filtered, washed with water, and dried under vacuum to yield carboxylic acid **11** (0.82 g, 96%) as a white solid: mp 183.5−185 °C; $^1$H NMR ($CDCl_3$) $\delta$ 7.45 (s, 1H), 7.40−7.30 (m, 2H), 6.98 (d, $J$ = 3.6 Hz, 1H), 6.69 (d, $J$ = 3.6 Hz, 1H), 2.42 (s, 3H), 2.39 (t, $J$ = 7.2 Hz,

2H), 1.61 (sextet, $J = 7.2$ Hz, 2H), 1.02 (t, $J = 7.2$ Hz, 3H); $^{13}$C NMR ($CDCl_3$) $\delta$ 165.7, 142.7, 137.6, 136.5, 135.6, 133.5, 131.0, 130.8, 130.1, 128.5, 128.2, 127.9, 126.8, 120.4, 96.7, 73.0, 21.9, 21.7, 13.5, 9.9. ESMS *m/z*: 419.0 (M + 1), 441 (M + 23). Anal. ($C_{20}H_{16}Cl_2N_2O_2S$) C, H, N.

**1-(2,4-Dichlorophenyl)-4-methyl-5-(5-(4-methylpent-1-ynyl)thiophen-2-yl)-1*H*-pyrazole-3-carboxylic Acid (11a).** According to the hydrolysis procedure applied to **11**, compound **11a** was obtained as a white solid (0.76 g, 96%): mp 186.5−188 °C; $^1$H NMR ($CDCl_3$) $\delta$ 7.47 (d, $J = 1.6$ Hz, 1H), 7.38−7.32 (m, 2H), 6.98 (d, $J = 4.0$ Hz, 1H), 6.70 (d, $J = 4.0$ Hz, 1H), 2.43 (s, 3H), 2.30 (d, $J = 6.4$ Hz, 1H), 1.89 (septet, $J = 6.4$ Hz, 1H), 1.01 (d, $J = 6.4$ Hz, 6H); $^{13}$C NMR ($CDCl_3$) $\delta$ 165.7, 137.6, 136.5, 135.6, 133.5, 131.0, 130.8, 130.1, 128.5, 128.2, 127.9, 126.9, 120.5, 95.9, 73.7, 28.8, 28.1, 22.1, 9.9. ESMS *m/z*: 433.0 (M + 1), 455.0 (M + 23). Anal. ($C_{21}H_{18}Cl_2N_2O_2S$) C, H, N.

**(*E*)-1-(2,4-Dichlorophenyl)-4-methyl-5-(5-(pent-1-enyl)thiophen-2-yl)-1*H*-pyrazole-3-carboxylic Acid (11b).** According to the hydrolysis procedure applied to **11**, compound **11b** was obtained as a white solid (0.29 g, 92%): mp 147−148 °C; $^1$H NMR ($CDCl_3$) $\delta$ 7.47 (s, 1H), 7.35 (s, 1H), 6.73 (d, $J = 3.9$ Hz, 1H), 6.67 (d, $J = 3.9$ Hz, 1H), 6.39 (d, $J = 15.9$ Hz, 1H), 6.03 (dt, $J = 15.9$, 7.2 Hz, 1H), 2.46 (s, 3H), 2.17−2.10 (m, 2H), 1.46 (sextet, $J = 7.2$ Hz, 2H), 0.93 (t, $J = 7.2$ Hz, 3H); $^{13}$C NMR ($CDCl_3$) $\delta$ 165.0, 145.7, 142.0, 138.5, 136.4, 135.8, 133.6, 132.7, 130.7, 130.1, 129.2, 127.8, 125.4, 124.2, 122.5, 120.2, 34.9, 22.2, 13.7, 9.9. ESMS *m/z*: 421.0 (M + 1), 443.0 (M + 23).

**5-(5-(But-1-ynyl)thiophen-2-yl)-1-(2,4-dichlorophenyl)-4-methyl-1*H*-pyrazole-3-carboxylic Acid (11c).** According to the hydrolysis procedure applied to **11**, compound **11c** was obtained as a white solid (0.70 g, 94%): mp 195.5−196.5 °C; $^1$H NMR ($CDCl_3$) $\delta$ 7.47 (s, 1H), 7.38−7.32 (m, 2H), 6.98 (d, $J = 3.6$ Hz, 1H), 6.72 (d, $J = 3.6$ Hz, 1H), 2.44 (s, 3H), 2.40 (q, $J = 5.4$ Hz, 2H), 1.20 (t, $J = 5.4$ Hz, 3H); $^{13}$C NMR ($CDCl_3$) $\delta$ 166.4, 142.0, 137.7, 136.6, 135.6, 133.6, 130.9, 130.7, 130.1, 128.6, 128.1, 127.9, 126.9, 120.7, 98.1, 72.2, 13.5, 13.4, 9.9. ESMS *m/z*: 405.0 (M + 1). Anal. ($C_{19}H_{14}Cl_2N_2O_2S$) C, H, N.

**1-(2,4-Dichlorophenyl)-5-(5-(hex-1-ynyl)thiophen-2-yl)-4-methyl-1*H*-pyrazole-3-carboxylic Acid (11d).** According to the hydrolysis procedure applied to **11**, compound **11d** was obtained as a white solid (0.79 g, 95%): mp 160−160.5 °C; $^1$H NMR ($CDCl_3$) $\delta$ 7.42 (d, $J = 8.1$ Hz, 1H), 7.34−7.20 (m, 2H), 6.92 (d, $J = 3.9$ Hz, 1H), 6.57 (d, $J = 3.9$ Hz, 1H), 2.40 (t, $J = 7.2$ Hz, 2H), 2.23 (s, 3H), 1.62−1.38 (m, 4H), 0.93 (t, $J = 7.2$ Hz, 3H); $^{13}$C NMR ($CDCl_3$) $\delta$ 166.4, 145.2, 136.7, 135.9, 135.7, 132.9, 131.2, 130.8, 129.8, 129.0, 128.1, 126.2, 119.5, 96.5, 73.0, 30.5, 22.0, 19.4, 13.6, 10.0. ESMS *m/z*: 433.0 (M + 1). Anal. ($C_{21}H_{18}Cl_2N_2O_2S$) C, H, N.

**1-(2,4-Dichlorophenyl)-5-(5-(3,3-dimethylbut-1-ynyl)thiophen-2-yl)-4-methyl-1*H*-pyrazole-3-carboxylic Acid (11e).** According to the hydrolysis procedure applied to **11**, compound **11e** was obtained as a white solid (0.78 g, 96%): mp 233.5−234 °C; $^1$H NMR ($CDCl_3$) $\delta$ 7.47 (d, $J = 2.0$ Hz, 1H), 7.38 (d, $J = 8.4$ Hz, 1H), 7.33 (dd, $J = 8.4$, 2.0 Hz, 1H), 6.97 (d, $J = 4.0$ Hz, 1H), 6.70 (d, $J = 4.0$ Hz, 1H), 2.44 (s, 3H), 1.29 (s, 9H); $^{13}$C NMR ($CDCl_3$) $\delta$ 166.5, 142.1, 137.7, 136.5, 135.6, 133.5, 131.0, 130.7, 130.1, 128.6, 128.0, 127.8, 126.9, 120.7, 104.5, 71.4, 30.6, 28.3, 9.9. ESMS *m/z*: 433.0 (M + 1), 455 (M + 23). Anal. ($C_{21}H_{18}Cl_2N_2O_2S$) Calcd: C 58.20; H 4.19; N 6.46. Found: C 58.66; H 4.47; N 6.46.

**5-(5-(Cyclopropylethynyl)thiophen-2-yl)-1-(2,4-dichlorophenyl)-4-methyl-1*H*-pyrazole-3-carboxylic Acid (11f).** According to the hydrolysis procedure applied to **11**, compound **11f** was obtained as a white solid (0.74 g, 93%): mp 136−138 °C; $^1$H NMR (DMSO-$d_6$) $\delta$ 7.86 (s, 1H), 7.72−7.58 (m, 2H), 7.14 (d, $J = 3.6$ Hz, 1H), 6.89 (d, $J = 3.6$ Hz, 1H), 2.33 (s, 3H), 1.60−1.50 (m, 1H), 0.98−0.80 (m, 2H), 0.78−0.66 (m, 2H); $^{13}$C NMR (DMSO-$d_6$) $\delta$ 164.3, 145.2, 136.1, 135.9, 135.5, 132.9, 132.0, 129.8, 129.0, 128.7, 128.6, 128.0, 125.2, 118.5, 100.2, 68.0, 10.0, 8.7, 0.0. ESMS *m/z*: 417.0 (M + 1), 439 (M + 23). Anal. ($C_{20}H_{14}Cl_2N_2O_2S$) Calcd: C 57.56; H 3.38; N 6.71. Found: C 56.88; H 4.29; N 6.70.

**5-(5-(Cyclopentylethynyl)thiophen-2-yl)-1-(2,4-dichlorophenyl)-4-methyl-1*H*-pyrazole-3-carboxylic Acid (11g).** According to the hydrolysis procedure applied to **11**, compound **11g** was obtained as a white solid (0.81 g, 96%): mp 197.5−199 °C; $^1$H NMR ($CDCl_3$) $\delta$ 7.42 (d, $J = 7.5$ Hz, 1H), 7.38−7.08 (m, 2H), 6.88 (d, $J = 3.6$ Hz, 1H), 6.49 (d, $J = 3.6$ Hz, 1H), 2.80 (q, $J = 7.5$ Hz, 1H), 2.14 (s, 3H), 2.10−1.50 (m, 8H); $^{13}$C NMR ($CDCl_3$) $\delta$ 167.1, 146.8, 136.5, 135.8, 135.6, 132.7, 131.2, 130.8, 129.7, 129.3, 128.1, 128.0, 126.1, 119.0, 100.3, 72.6, 33.6, 31.0, 25.1, 10.1. ESMS *m/z*: 467.0 (M + 23). Anal. ($C_{22}H_{18}Cl_2N_2O_2S$) C, H, N.

**5-(5-(Cyclohexylethynyl)thiophen-2-yl)-1-(2,4-dichlorophenyl)-4-methyl-1*H*-pyrazole-3-carboxylic Acid (11h).** According to the hydrolysis procedure applied to **11**, compound **11h** was obtained as a white solid (0.79 g, 94%): mp 212.5−213 °C; $^1$H NMR ($CDCl_3$) $\delta$ 7.48 (s, 1H), 7.40−7.30 (m, 2H), 6.98 (d, $J = 3.6$ Hz, 1H), 6.71 (d, $J = 3.6$ Hz, 1H), 2.68−2.52 (m, 1H), 2.45 (s, 3H), 1.90−1.61 (m, 4H), 1.60−1.20 (m, 6H); $^{13}$C NMR (DMSO-$d_6$) $\delta$ 163.5, 143.1, 136.4, 135.6, 135.5, 132.7, 131.8, 131.6, 129.7, 129.3, 128.5, 128.1, 125.4, 119.0, 100.6, 72.7, 31.8, 29.0, 25.2, 24.3, 9.7. ESMS *m/z*: 459.2 (M + 1).

**1-(2,4-Dichlorophenyl)-4-methyl-5-(5-(pent-1-ynyl)thiophen-2-yl)-*N*-(piperidin-1-yl)-1*H*-pyrazole-3-carboxamide (12).** To a mixture of carboxylic acid **11** (84 mg, 0.20 mmol) and triethylamine (84 $\mu$L, 0.60 mmol) in dichloromethane (4 mL) at 0 °C was added trimethylacetyl chloride (48 $\mu$L, 0.40 mmol) slowly. The mixture was allowed to warm to room temperature and stirred for 2 h. The carboxylic anhydride thus formed was introduced into a mixture of 1-aminopiperidine (44 $\mu$L, 0.40 mmol) and triethylamine (84 $\mu$L, 0.60 mmol) in dichloromethane (5 mL) at 0 °C. After the mixture was stirred at room temperature for 2 h, the reaction was quenched with water and the aqueous solution was separated and extracted with dichloromethane (2 × 10 mL). The combined extracts were washed with brine, dried over anhydrous sodium sulfate, filtered, and evaporated. Flash chromatography of the crude product on silica gel with *n*-hexane/ethyl acetate (5:1) gave carboxamide **12** (73 mg, 73% over two steps) as a white solid: mp 79−81 °C; $^1$H NMR ($CDCl_3$) $\delta$ 7.60 (s, 1H), 7.49 (s, 1H), 7.37−7.26 (m, 2H), 6.97 (d, $J = 3.6$ Hz, 1H), 6.68 (d, $J = 3.6$ Hz, 1H), 2.90−2.80 (m, 4H), 2.46 (s, 3H), 2.38 (t, $J = 6.9$ Hz, 2H), 1.78−1.70 (m, 4H), 1.53 (sextet, $J = 6.9$ Hz, 2H), 1.48−1.36 (m, 2H), 1.01 (t, $J = 6.9$ Hz, 3H); $^{13}$C NMR ($CDCl_3$) $\delta$ 159.5, 144.1, 137.1, 136.2, 135.6, 133.5, 130.8, 130.6, 130.0, 128.3, 128.0, 127.7, 126.4, 118.9, 96.4, 72.8, 56.8, 25.2, 23.1, 21.7, 21.4, 13.3, 9.4. ESMS *m/z*: 501.1 (M + 1). Anal. ($C_{25}H_{26}Cl_2N_4OS$) C, H, N.

**1-(2,4-Dichlorophenyl)-*N*-(hexahydrocyclopenta[*c*]pyrrol-2(1*H*)-yl)-4-methyl-5-(5-(pent-1-ynyl)thiophen-2-yl)-1*H*-pyrazole-3-carboxamide (13).** Using carboxylic acid **11** (84 mg, 0.20 mmol) as a starting material, carboxamide **13** was synthesized following a similar coupling procedure for **12** as a white solid (76 mg, 72%): mp 148−149.5 °C; $^1$H NMR ($CDCl_3$) $\delta$ 7.50 (s, 1H), 7.42 (s, 1H), 7.36−7.26 (m, 2H), 6.91 (d, $J = 3.3$ Hz, 1H), 6.63 (d, $J = 3.3$ Hz, 1H), 3.18 (t, $J = 6.6$ Hz, 2H), 2.71−2.51 (m, 2H), 2.41 (s, 3H), 2.31 (t, $J = 6.6$ Hz, 2H), 1.70−1.36 (m, 10H), 0.95 (t, $J = 6.6$ Hz, 3H); $^{13}$C NMR ($CDCl_3$) $\delta$ 160.2, 144.1, 137.1, 136.2, 135.6, 133.5, 130.8, 130.6, 130.0, 128.3, 128.0, 127.7, 126.4, 118.8, 96.4, 72.9, 62.3, 40.2, 32.1, 25.4, 21.7, 21.4, 13.4, 9.4. ESMS *m/z*: 527.1 (M + 1). Anal. ($C_{27}H_{28}Cl_2N_4OS$) C, H, N.

***N*-(Azepan-1-yl)-1-(2,4-dichlorophenyl)-4-methyl-5-(5-(pent-1-ynyl)thiophen-2-yl)-1*H*-pyrazole-3-carboxamide (14).** Using carboxylic acid **11** (84 mg, 0.20 mmol) as a starting material, carboxamide **14** was synthesized following a similar coupling procedure for **12** as a white solid (67 mg, 65%): mp 64−65 °C; $^1$H NMR ($CDCl_3$) $\delta$ 8.05 (s, 1H), 7.49 (d, $J = 2.0$ Hz, 1H), 7.38−7.28 (m, 2H), 6.97 (d, $J = 4.0$ Hz, 1H), 6.69 (d, $J = 4.0$ Hz, 1H), 3.14 (t, $J = 5.6$ Hz, 4H), 2.40 (s, 3H), 2.38 (t, $J = 7.2$ Hz, 2H), 1.80−1.60 (m, 8H), 1.60 (sextet, $J = 7.2$ Hz, 2H), 1.01 (t, $J = 7.2$ Hz, 3H); $^{13}$C NMR ($CDCl_3$) $\delta$ 160.1, 144.3, 137.3, 136.3, 135.8, 133.7, 130.9, 130.7, 130.2, 128.6, 128.2, 127.9, 126.5, 119.1, 96.6, 73.0, 58.3, 26.9, 26.3, 21.9, 21.6, 13.5, 9.6. ESMS *m/z*: 515.1 (M + 1). Anal. ($C_{26}H_{28}Cl_2N_4OS$) C, H, N.

**1-(2,4-Dichlorophenyl)-4-methyl-5-(5-(4-methylpent-1-ynyl)thiophen-2-yl)-*N*-(piperidin-1-yl)-1*H*-pyrazole-3-carboxamide (15).** Using carboxylic acid **11a** (130 mg, 0.30 mmol) as a starting material, carboxamide **15** was synthesized following a similar coupling procedure for **12** as a white solid (108 mg, 70%): mp 101.5−103 °C; $^1$H NMR ($CDCl_3$) $\delta$ 7.61 (s, 1H), 7.49 (d, $J$ = 2.0 Hz, 1H), 7.34 (d, $J$ = 2.0 Hz, 2H), 6.97 (d, $J$ = 3.6 Hz, 1H), 6.68 (d, $J$ = 3.6 Hz, 1H), 2.91−2.80 (m, 4H), 2.47 (s, 3H), 2.29 (d, $J$ = 6.4 Hz, 2H), 1.94−1.82 (m, 1H), 1.80−1.70 (m, 4H), 1.44−1.40 (m, 2H), 1.01 (d, $J$ = 6.4 Hz, 6H); $^{13}$C NMR ($CDCl_3$) $\delta$ 159.8, 144.3, 137.3, 136.4, 135.8, 133.7, 130.9, 130.8, 130.3, 128.5, 128.2, 127.9, 126.6, 119.2, 95.7, 73.7, 57.0, 28.8, 28.0, 25.4, 23.3, 22.0, 9.9. ESMS *m*/*z*: 515.1 (M + 1). Anal. ($C_{26}H_{28}Cl_2N_4OS$) C, H, N.

***N*-(Azepan-1-yl)-1-(2,4-dichlorophenyl)-4-methyl-5-(5-(4-methylpent-1-ynyl)thiophen-2-yl)-1*H*-pyrazole-3-carboxamide (16).** Using carboxylic acid **11a** (125 mg, 0.29 mmol) as a starting material, carboxamide **16** was synthesized following a similar coupling procedure for **12** as a white solid (101 mg, 66%): mp 48−49 °C; $^1$H NMR ($CDCl_3$) $\delta$ 8.03 (s, 1H), 7.48 (d, $J$ = 1.2 Hz, 1H), 7.40−7.30 (m, 2H), 6.96 (d, $J$ = 3.6 Hz, 1H), 6.67 (d, $J$ = 3.6 Hz, 1H), 3.13 (t, $J$ = 5.4 Hz, 4H), 2.46 (s, 3H), 2.29 (d, $J$ = 6.9 Hz, 2H), 1.96−1.80 (m, 1H), 1.80−1.60 (m, 8H), 1.00 (d, $J$ = 6.4 Hz, 6H); $^{13}$C NMR ($CDCl_3$) $\delta$ 160.0, 144.2, 137.2, 136.2, 135.7, 133.6, 130.9, 130.7, 130.2, 128.5, 128.1, 127.8, 126.5, 119.0, 95.7, 73.7, 58.2, 28.7, 28.0, 26.8, 26.2, 22.0, 9.6. ESMS *m*/*z*: 529.2 (M + 1). Anal. ($C_{27}H_{30}Cl_2N_4OS$) C, H, N.

**1-(2,4-Dichlorophenyl)-4-methyl-5-(5-pentylthiophen-2-yl)-1*H*-pyrazole-3-carboxylic acid (17).** A mixture of carboxylic acid **11** (0.84 g, 2.00 mmol) and 10% Pd/C (80 mg) in MeOH (10 mL) was stirred under hydrogen (1 atm) at room temperature for 24 h. After the reaction was complete, the mixture was filtered through Celite, washed with MeOH, and concentrated under vacuum to afford carboxylic acid **17** (0.38 g, 45%): mp 170−171 °C; $^1$H NMR ($CDCl_3$) $\delta$ 10.15 (br s, 1H), 7.39 (d, $J$ = 8.4 Hz, 1H), 7.36 (d, $J$ = 1.8 Hz, 1H), 7.27 (dd, $J$ = 8.4, 1.8 Hz, 1H), 6.62 (s, 2H), 2.71 (t, $J$ = 7.5 Hz, 2H), 2.34 (s, 3H), 1.61 (m, 2H), 1.40−1.20 (m, 4H), 0.88 (t, $J$ = 7.2 Hz, 3H); $^{13}$C NMR ($CDCl_3$) $\delta$ 166.5, 148.5, 143.5, 138.2, 136.0, 135.9, 133.4, 131.0, 129.7, 128.5, 127.7, 125.9, 124.0, 119.4, 31.1, 31.0, 29.8, 22.3, 13.9, 10.0. ESMS *m*/*z*: 423.1(M + 1), 445.1 (M + 23). Anal. ($C_{20}H_{20}Cl_2N_2O_2S$) Calcd: C 56.74; H 4.76; N 6.62. Found: C 55.39; H 4.71; N 6.22.

**1-(2,4-Dichlorophenyl)-4-ethyl-5-(5-(pent-1-ynyl)thiophen-2-yl)-*N*-(piperidin-1-yl)-1*H*-pyrazole-3-carboxamide (18).** Using 1-(2,4-dichlorophenyl)-4-ethyl-5-(5-(4-methylpent-1-ynyl)thiophen-2-yl)-1*H*-pyrazole-3-carboxylic acid (104 mg, 0.24 mmol) as a starting material, compound **18** was synthesized following a similar coupling procedure for **12** as a white solid (80 mg, 65%): mp 88.5−89.5 °C; $^1$H NMR ($CDCl_3$) $\delta$ 7.63 (s, 1H), 7.47 (dd, $J$ = 2.4, 1.2 Hz, 1H), 7.34−7.32 (m, 2H), 6.96 (d, $J$ = 3.6 Hz, 1H), 6.67 (d, $J$ = 3.6 Hz, 1H), 2.91 (q, $J$ = 7.5 Hz, 2H), 2.90−2.78 (m, 4H), 2.38 (t, $J$ = 7.2 Hz, 2H), 1.80−1.70 (m, 4H), 1.60 (sextet, $J$ = 7.2 Hz, 2H), 1.48−1.36 (m, 2H), 1.25 (t, $J$ = 7.5 Hz, 3H), 1.02 (t, $J$ = 7.2 Hz, 3H); $^{13}$C NMR ($CDCl_3$) $\delta$ 159.4, 143.9, 136.8, 136.3, 135.8, 133.7, 131.0, 130.7, 130.2, 128.4, 128.3, 127.8, 126.7, 126.0, 96.5, 73.0, 57.0, 25.4, 23.3, 21.8, 21.6, 17.2, 15.7, 13.5. ESMS *m*/*z*: 515.1 (M + 1), 537.1 (M + 23). Anal. ($C_{26}H_{28}Cl_2N_4OS$) C, H, N.

***N*-(Azepan-1-yl)-1-(2,4-dichlorophenyl)-4-ethyl-5-(5-(pent-1-ynyl)thiophen-2-yl)-1*H*-pyrazole-3-carboxamide (19).** Using 1-(2,4-dichlorophenyl)-4-ethyl-5-(5-(4-methylpent-1-ynyl)thiophen-2-yl)-1*H*-pyrazole-3-carboxylic acid (121 mg, 0.28 mmol) as a starting material, compound **19** was synthesized following a similar coupling procedure for **14** as a white solid (98 mg, 66%): mp 58−60 °C; $^1$H NMR ($CDCl_3$) $\delta$ 8.05 (s, 1H), 7.47 (s, 1H), 7.37−7.27 (m, 2H), 6.96 (d, $J$ = 3.6 Hz, 1H), 6.67 (d, $J$ = 3.6 Hz, 1H), 3.13 (t, $J$ = 5.4 Hz, 4H), 2.88 (q, $J$ = 7.5 Hz, 2H), 2.38 (t, $J$ = 7.2 Hz, 2H), 1.79−1.68 (m, 4H), 1.68−1.54 (m, 6H), 1.25 (t, $J$ = 7.5 Hz, 3H), 1.02 (t, $J$ = 7.2 Hz, 3H); $^{13}$C NMR ($CDCl_3$) $\delta$ 159.7, 143.9, 136.7, 136.2, 135.7, 133.6, 130.9, 130.6, 130.1, 128.4, 128.2, 127.8, 126.6, 125.8, 96.5, 72.9, 58.3, 26.8, 26.3, 21.8, 21.6, 17.1, 15.7, 13.5. ESMS *m*/*z*: 529.1 (M + 1), 551.1 (M + 23). Anal. ($C_{27}H_{30}Cl_2N_4OS$) Calcd: C 61.24; H 5.71; N 10.58. Found: C 61.70; H 6.17; N 10.68.

**1-(2,4-Dichlorophenyl)-4-ethyl-5-(5-(4-methylpent-1-ynyl)thiophen-2-yl)-*N*-(piperidin-1-yl)-1*H*-pyrazole-3-carboxamide (20).** Using 1-(2,4-dichlorophenyl)-4-ethyl-5-(5-(4-methylpent-1-ynyl)thiophen-2-yl)-1*H*-pyrazole-3-carboxylic acid (134 mg, 0.30 mmol) as a starting material, compound **20** was synthesized following a similar coupling procedure for **12** as a white solid (103 mg, 65%): mp 92−93 °C; $^1$H NMR ($CDCl_3$) $\delta$ 7.63 (s, 1H), 7.48 (d, $J$ = 1.5 Hz, 1H), 7.35−7.33 (m, 2H), 6.96 (d, $J$ = 3.9 Hz, 1H), 6.66 (d, $J$ = 3.9 Hz, 1H), 2.87 (q, $J$ = 7.5 Hz, 2H), 2.86−2.84 (m, 4H), 2.30 (d, $J$ = 6.6 Hz, 2H), 1.89 (septet, $J$ = 6.6 Hz, 1H), 1.79−1.71 (m, 4H), 1.50−1.38 (m, 2H), 1.26 (t, $J$ = 7.5 Hz, 3H), 1.01 (d, $J$ = 6.6 Hz, 6H); $^{13}$C NMR ($CDCl_3$) $\delta$ 159.4, 143.9, 136.8, 136.2, 135.8, 133.6, 131.0, 130.7, 130.2, 128.4, 128.3, 127.8, 126.7, 126.0, 95.7, 73.7, 57.0, 28.8, 28.0, 25.4, 23.3, 22.0, 17.2, 15.7. ESMS *m*/*z*: 529.2 (M + 1), 551.1 (M + 23). Anal. ($C_{27}H_{30}Cl_2N_4OS$) C, H, N.

**1-(2,4-Dichlorophenyl)-4-methyl-5-[((*E*)-5-pent-1-enyl)-thiophen-2-yl]-1*H*-pyrazole-3-carboxylic Acid Piperidin-1-ylamide (21).** Starting from the carboxylic acid **11b** (130 mg, 0.30 mmol), compound **21** was synthesized following a similar coupling procedure for **12** and obtained as a white solid (110 mg, 73%): mp 71−71.5 °C; $^1$H NMR ($CDCl_3$) $\delta$ 7.61 (s, 1H), 7.49 (d, $J$ = 1.2 Hz, 1H), 7.35−7.33 (m, 2H), 6.71 (d, $J$ = 3.6 Hz, 1H), 6.64 (d, $J$ = 3.6 Hz, 1H), 6.39 (d, $J$ = 15.9 Hz, 1H), 6.02 (dt, $J$ = 15.9, 6.9 Hz, 1H), 2.87−2.84 (m, 4H), 2.47 (s, 3H), 2.20−2.06 (m, 2H), 1.79−1.71 (m, 4H), 1.50−1.38 (m, 4H), 0.93 (t, $J$ = 7.2 Hz, 3H); $^{13}$C NMR ($CDCl_3$) $\delta$ 159.9, 145.4, 144.2, 138.0, 136.1, 136.0, 133.7, 132.4, 130.8, 130.2, 128.8, 127.8, 125.9, 124.1, 122.5, 118.9, 57.0, 34.9, 25.4, 23.3, 22.2, 13.7, 9.6. ESMS *m*/*z*: 503.1 (M + 1), 525.1 (M + 23). Anal. ($C_{25}H_{28}Cl_2N_4OS$) C, H, N.

**1-(2,4-Dichlorophenyl)-4-methyl-5-[((*E*)-5-pent-1-enyl)-thiophen-2-yl]-1*H*-pyrazole-3-carboxylic acid (hexahydrocyclopenta[*c*]pyrrol-2-yl)amide (22).** Starting from the carboxylic acid **11b** (130 mg, 0.30 mmol), compound **22** was synthesized following a similar coupling procedure for **13** and obtained as a white solid (114 mg, 72%): mp 124−124.5 °C; $^1$H NMR ($CDCl_3$) $\delta$ 7.49 (s, 1H), 7.48 (s, 1H), 7.33−7.32 (m, 2H), 6.71 (d, $J$ = 3.6 Hz, 1H), 6.64 (d, $J$ = 3.6 Hz, 1H), 6.38 (d, $J$ = 15.6 Hz, 1H), 6.02 (dt, $J$ = 15.6, 6.6 Hz, 1H), 3.28 (t, $J$ = 7.5 Hz, 2H), 2.56−2.47 (m, 2H), 2.47 (s, 3H), 2.16−2.07 (m, 2H), 1.78−1.42 (m, 10H), 0.93 (t, $J$ = 7.2 Hz, 3H); $^{13}$C NMR ($CDCl_3$) $\delta$ 160.6, 145.4, 144.1, 138.0, 136.2, 136.0, 133.7, 132.4, 130.7, 130.2, 128.8, 127.8, 125.8, 124.1, 122.5, 118.8, 62.4, 40.4, 34.9, 32.3, 25.6, 22.2, 13.7, 9.6. ESMS *m*/*z*: 529.1 (M + 1), 551.1 (M + 23). Anal. ($C_{27}H_{30}Cl_2N_4OS$) C, H, N.

**1-(2,4-Dichlorophenyl)-4-methyl-5-(5-pentylthiophen-2-yl)-*N*-(piperidin-1-yl)-1*H*-pyrazole-3-carboxamide (23).** Starting from the carboxylic acid **17** (127 mg, 0.30 mmol), compound **23** was synthesized following a similar coupling procedure for **12** and obtained as a white solid (115 mg, 75%): mp 70−71 °C; $^1$H NMR ($CDCl_3$) $\delta$ 7.61 (s, 1H), 7.48 (d, $J$ = 0.9 Hz, 1H), 7.35−7.31 (m, 2H), 6.62−6.68 (m, 2H), 2.85 (t, $J$ = 6.4 Hz, 4H), 2.72 (t, $J$ = 7.5 Hz, 2H), 2.47 (s, 3H), 1.79−1.71 (m, 4H), 1.70−1.58 (m, 2H), 1.50−1.36 (m, 2H), 1.36−1.22 (m, 4H), 0.88 (t, $J$ = 7.5 Hz, 3H); $^{13}$C NMR ($CDCl_3$) $\delta$ 159.9, 148.6, 144.1, 138.3, 136.1, 136.0, 133.8, 130.8, 130.1, 128.4, 127.7, 125.9, 124.1, 118.5, 57.0, 31.1, 30.9, 29.8, 25.3, 23.3, 22.3, 13.9, 9.6. ESMS *m*/*z*: 505.2 (M + 1). Anal. ($C_{25}H_{30}Cl_2N_4OS$) C, H, N.

**1-(2,4-Dichlorophenyl)-*N*-(hexahydrocyclopenta[*c*]pyrrol-2(1*H*)-yl)-4-methyl-5-(5-pentylthiophen-2-yl)-1*H*-pyrazole-3-carboxamide (24).** Starting from the carboxylic acid **17** (127 mg, 0.30 mmol), compound **24** was synthesized following a similar coupling procedure for **13** and obtained as a white solid (107 mg, 67%): mp 123−123.5 °C; $^1$H NMR ($CDCl_3$) $\delta$ 7.50−7.45 (m, 2H), 7.33−7.30 (m, 2H), 6.68−6.62 (m, 2H), 3.27 (t, $J$ = 8.1 Hz, 2H), 2.72 (t, $J$ = 7.5 Hz, 2H), 2.70−2.62 (m, 2H), 2.53−2.47 (m, 4H), 2.47 (s, 3H), 1.75−1.40 (m, 6H), 1.38−1.21 (m, 4H), 0.88 (t, $J$ = 6.6 Hz, 3H); $^{13}$C NMR ($CDCl_3$) $\delta$ 160.7, 148.6, 144.1, 138.3, 136.1, 136.0, 133.8, 130.8, 130.1, 128.4, 127.7, 125.9, 124.1, 118.4, 62.5, 40.4, 32.3, 31.1, 31.0, 29.8, 25.6, 22.2, 13.9, 9.6. ESMS *m*/*z*: 531.2 (M + 1). Anal. ($C_{27}H_{32}Cl_2N_4OS$) C, H, N.

**5-(5-(But-1-ynyl)thiophen-2-yl)-1-(2,4-dichlorophenyl)-4-methyl-*N*-(piperidin-1-yl)-1*H*-pyrazole-3-carboxamide (25).** Starting from carboxylic acid **11c** (89 mg, 0.22 mmol), compound **25** was synthesized following a similar coupling procedure for **12** and obtained as a white solid (75 mg, 70%): mp 81−82 °C; $^1$H NMR ($CDCl_3$) $\delta$ 7.64 (s, 1H), 7.49 (d, $J$ = 0.9 Hz, 1H), 7.36−7.32 (m, 2H), 6.98 (d, $J$ = 3.6 Hz, 1H), 6.70 (d, $J$ = 3.6 Hz, 1H), 2.90−2.80 (m, 4H), 2.47 (s, 3H), 2.42 (q, $J$ = 7.2 Hz, 2H), 1.80−1.72 (m, 4H), 1.48−1.38 (m, 2H), 1.21 (t, $J$ = 7.2 Hz, 3H); $^{13}$C NMR ($CDCl_3$) $\delta$ 159.7, 144.2, 137.3, 136.3, 135.7, 133.7, 130.9, 130.7, 130.2, 128.5, 128.2, 127.9, 126.5, 119.2, 97.8, 72.2, 57.0, 25.3, 23.3, 13.5, 13.3, 9.6. ESMS *m*/*z*: 487.2 (M + 1). Anal. ($C_{24}H_{24}Cl_2N_4OS$) C, H, N.

**5-(5-(But-1-ynyl)thiophen-2-yl)-1-(2,4-dichlorophenyl)-*N*-(hexahydrocyclopenta[*c*]pyrrol-2(1*H*)-yl)-4-methyl-1*H*-pyrazole-3-carboxamide (26).** Starting from carboxylic acid **11c** (90 mg, 0.22 mmol), compound **26** was synthesized following a similar coupling procedure for **13** and obtained as a white solid (81 mg, 72%): mp 79−80 °C; $^1$H NMR ($CDCl_3$) $\delta$ 7.52 (s, 1H), 7.47 (d, $J$ = 1.6 Hz, 1H), 7.38−7.34 (m, 2H), 6.97 (d, $J$ = 4.0 Hz, 1H), 6.69 (d, $J$ = 4.0 Hz, 1H), 3.25 (t, $J$ = 8.0 Hz, 2H), 2.57−2.47 (m, 2H), 2.47 (s, 3H), 2.40 (q, $J$ = 7.6 Hz, 2H), 1.74−1.60 (m, 4H), 1.60−1.42 (m, 4H), 1.19 (t, $J$ = 7.6 Hz, 3H); $^{13}$C NMR ($CDCl_3$) $\delta$ 160.2, 144.1, 136.8, 136.4, 135.4, 133.5, 130.9, 130.6, 130.1, 130.0, 128.4, 128.1, 126.4, 119.1, 97.8, 72.2, 62.4, 40.3, 32.1, 25.4, 13.4, 13.2, 9.4. ESMS *m*/*z*: 513.1 (M + 1). Anal. ($C_{26}H_{26}Cl_2N_4OS$) C, H, N.

***N*-(Azepan-1-yl)-5-(5-(but-1-ynyl)thiophen-2-yl)-1-(2,4-dichlorophenyl)-4-methyl-1*H*-pyrazole-3-carboxamide (27).** Starting from carboxylic acid **11c** (122 mg, 0.30 mmol), compound **27** was synthesized following a similar coupling procedure for **14** and obtained as a white solid (102 mg, 68%): mp 73−74 °C; $^1$H NMR ($CDCl_3$) $\delta$ 8.04 (s, 1H), 7.49 (d, $J$ = 1.6 Hz, 1H), 7.38−7.28 (m, 2H), 6.98 (d, $J$ = 4.0 Hz, 1H), 6.70 (d, $J$ = 4.0 Hz, 1H), 3.13 (t, $J$ = 5.6 Hz, 4H), 2.47 (s, 3H), 2.41 (q, $J$ = 7.6 Hz, 2H), 1.80−1.60 (m, 8H), 1.21 (t, $J$ = 7.6 Hz, 3H); $^{13}$C NMR ($CDCl_3$) $\delta$ 160.2, 144.2, 137.3, 136.4, 135.7, 133.7, 130.9, 130.7, 130.3, 128.6, 128.2, 127.9, 126.5, 119.1, 97.9, 72.3, 63.8, 58.4, 26.9, 26.1, 13.5, 9.6. ESMS *m*/*z*: 501.1 (M + 1). Anal. ($C_{25}H_{26}Cl_2N_4OS$) C, H, N.

**1-(2,4-Dichlorophenyl)-5-(5-(hex-1-ynyl)thiophen-2-yl)-4-methyl-*N*-(piperidin-1-yl)-1*H*-pyrazole-3-carboxamide (28).** Starting from carboxylic acid **11d** (108 mg, 0.25 mmol), compound **28** was synthesized following a similar coupling procedure for **12** and obtained as a white solid (94 mg, 73%): mp 68−69 °C; $^1$H NMR ($CDCl_3$) $\delta$ 7.62 (s, 1H), 7.48 (s, 1H), 7.36−7.26 (m, 2H), 6.97 (d, $J$ = 3.6 Hz, 1H), 6.69 (d, $J$ = 3.6 Hz, 1H), 2.90−2.77 (m, 4H), 2.47 (s, 3H), 2.40 (t, $J$ = 7.2 Hz, 2H), 1.80−1.70 (m, 4H), 1.60−1.38 (m, 6H), 0.93 (t, $J$ = 7.2 Hz, 3H); $^{13}$C NMR ($CDCl_3$) $\delta$ 159.7, 144.3, 137.3, 136.3, 135.7, 133.7, 130.9, 130.7, 130.2, 128.5, 128.1, 127.9, 126.5, 119.1, 96.7, 72.8, 56.9, 30.4, 25.3, 23.3, 21.9, 19.3, 13.5, 9.6. ESMS *m*/*z*: 515.1 (M + 1). Anal. ($C_{26}H_{28}Cl_2N_4OS$) C, H, N.

**1-(2,4-Dichlorophenyl)-5-(5-(hex-1-ynyl)thiophen-2-yl)-*N*-(hexahydrocyclopenta[*c*]pyrrol-2(1*H*)-yl)-4-methyl-1*H*-pyrazole-3-carboxamide (29).** Starting from carboxylic acid **11d** (108 mg, 0.25 mmol), compound **29** was synthesized following a similar coupling procedure for **13** and obtained as a white solid (96 mg, 71%): mp 145−146 °C; $^1$H NMR ($CDCl_3$) $\delta$ 7.50 (s, 1H), 7.48 (s, 1H), 7.38−7.28 (m, 2H), 6.96 (d, $J$ = 3.6 Hz, 1H), 6.69 (d, $J$ = 3.6 Hz, 1H), 3.30−3.21 (m, 2H), 2.56−2.46 (m, 2H), 2.47 (s, 3H), 2.40 (t, $J$ = 7.2 Hz, 2H), 1.72−1.40 (m, 12H), 0.91 (t, $J$ = 7.2 Hz, 3H); $^{13}$C NMR ($CDCl_3$) $\delta$ 160.4, 144.2, 137.3, 136.3, 135.7, 133.7, 130.9, 130.7, 130.2, 128.5, 128.1, 127.8, 126.5, 119.0, 96.7, 72.8, 62.5, 40.4, 32.2, 30.4, 25.5, 21.9, 19.3, 13.5, 9.6. ESMS *m*/*z*: 541.1 (M + 1). Anal. ($C_{28}H_{30}Cl_2N_4OS$) C, H, N.

***N*-(Azepan-1-yl)-1-(2,4-dichlorophenyl)-5-(5-(hex-1-ynyl)thiophen-2-yl)-4-methyl-1*H*-pyrazole-3-carboxamide (30).** Starting from carboxylic acid **11d** (108 mg, 0.25 mmol), compound **30** was synthesized following a similar coupling procedure for **14** and obtained as a white solid (87 mg, 66%): mp 63−64.5 °C; $^1$H NMR ($CDCl_3$) $\delta$ 8.06 (s, 1H), 7.48 (s, 1H), 7.40−7.26 (m, 2H), 6.96 (d, $J$ = 4.0 Hz, 1H), 6.68 (d, $J$ = 4.0 Hz, 1H), 3.20−3.08 (m, 4H), 2.46 (s, 3H), 2.44−2.38 (m, 2H), 1.81−1.58 (m, 8H), 1.58−1.40 (m, 4H), 0.92 (t, $J$ = 3.6 Hz, 3H); $^{13}$C NMR ($CDCl_3$) $\delta$ 160.0, 144.3, 137.2, 136.3, 135.7, 133.6, 130.9, 130.7, 130.2, 128.5, 128.1, 127.8, 126.5, 119.0, 96.7, 72.8, 58.2, 30.4, 26.9, 26.2, 21.9, 19.3, 13.5, 9.6. ESMS *m*/*z*: 529.1 (M + 1). Anal. ($C_{27}H_{30}Cl_2N_4OS$) Calcd: C 61.24; H 5.71; N 10.58. Found: C 59.92; H 5.62; N 10.92.

***N*-Butyl-1-(2,4-dichlorophenyl)-5-(5-(hex-1-ynyl)thiophen-2-yl)-4-methyl-1*H*-pyrazole-3-carboxamide (31).** To a mixture of carboxylic acid **11d** (108 mg, 0.25 mmol) and triethylamine (0.11 mL, 0.75 mmol) in dichloromethane (5 mL) stirred at 0 °C, trimethylacetyl chloride (60 $\mu$L, 0.50 mmol) was added slowly at 0 °C and allowed to warm to room temperature for 2 h. The carboxylic anhydride thus formed was delivered into a mixture of butan-1-amine (50 $\mu$L, 0.50 mmol) and triethylamine (0.11 mL, 0.75 mmol) in 5 mL of dichloromethane at 0 °C. After the mixture was stirred at room temperature for 2 h, the reaction was quenched with water and the aqueous layer was separated and extracted with dichloromethane (3 × 10 mL). The combined extracts were washed with brine, dried over anhydrous sodium sulfate, filtered, and evaporated. Flash column chromatography of the crude product on silica gel with *n*-hexane/ethyl acetate (5:1) gave carboxamide **31** (85 mg, 70%) as a white solid: mp 81−82.5 °C; $^1$H NMR ($CDCl_3$) $\delta$ 7.43 (s, 1H), 7.40−7.20 (m, 2H), 7.00−6.92 (br, 1H), 6.92 (d, $J$ = 3.9 Hz, 1H), 6.68 (d, $J$ = 3.9 Hz, 1H), 3.34 (t, $J$ = 6.6 Hz, 2H), 2.44 (s, 3H), 2.35 (t, $J$ = 6.6 Hz, 2H), 1.60−1.22 (m 8H), 0.98−0.80 (m, 6H); $^{13}$C NMR ($CDCl_3$) $\delta$ 162.2, 144.8, 137.2, 136.2, 135.7, 133.5, 130.8, 130.6, 130.1, 128.5, 128.0, 127.7, 126.4, 118.4, 96.5, 72.8, 38.5, 31.6, 30.3, 21.8, 20.0, 19.2, 13.6, 13.4, 9.5. ESMS *m*/*z*: 488.1 (M + 1). Anal. ($C_{25}H_{27}Cl_2N_3OS$) C, H, N.

**1-(2,4-Dichlorophenyl)-5-(5-(hex-1-ynyl)thiophen-2-yl)-*N*-hexyl-4-methyl-1*H*-pyrazole-3-carboxamide (32).** Starting from carboxylic acid **11d** (108 mg, 0.25 mmol), compound **32** was synthesized following a similar coupling procedure for **31** and obtained as a white solid (93 mg, 72%): mp 66−67 °C; $^1$H NMR ($CDCl_3$) $\delta$ 7.50 (d, $J$ = 6.4 Hz, 1H), 7.40−7.28 (m, 2H), 7.00−6.90 (m, 2H), 6.70 (d, $J$ = 3.9 Hz, 1H), 3.41 (t, $J$ = 6.4 Hz, 2H), 2.49 (s, 3H), 2.42 (t, $J$ = 6.4 Hz, 2H), 1.64−1.22 (m, 12H), 1.00−0.82 (m, 6H); $^{13}$C NMR ($CDCl_3$) $\delta$ 162.4, 145.0, 137.4, 136.3, 135.8, 133.7, 130.9, 130.7, 130.3, 128.6, 128.2, 127.9, 126.5, 118.7, 96.7, 72.9, 39.0, 31.5, 30.4, 29.6, 26.6, 22.5, 21.9, 19.4, 14.0, 13.6, 9.7. ESMS *m*/*z*: 516.2 (M + 1). Anal. ($C_{27}H_{31}Cl_2N_3OS$) C, H, N.

***N*-Cyclohexyl-1-(2,4-dichlorophenyl)-5-(5-(hex-1-ynyl)thiophen-2-yl)-4-methyl-1*H*-pyrazole-3-carboxamide (33).** Starting from carboxylic acid **11d** (108 mg, 0.25 mmol), compound **33** was synthesized following a similar coupling procedure for **31** and obtained as a white solid (90 mg, 70%): mp 125.5−126 °C; $^1$H NMR ($CDCl_3$) $\delta$ 7.49 (s, 1H), 7.40−7.28 (m, 2H), 6.96 (d, $J$ = 4.4 Hz, 1H), 6.69 (d, $J$ = 4.4 Hz, 1H), 4.00−3.86 (m, 1H), 2.48 (s, 3H), 2.40 (t, $J$ = 7.2 Hz, 2H), 2.15−1.96 (m, 2H), 1.78−1.70 (m, 2H), 1.68−1.14 (m, 10H), 0.92 (t, $J$ = 7.2 Hz, 3H); $^{13}$C NMR ($CDCl_3$) $\delta$ 161.9, 145.4, 137.6, 136.6, 136.1, 134.0, 131.2, 131.1, 130.5, 129.0, 128.4, 128.2, 126.8, 119.0, 96.9, 73.2, 48.2, 33.4, 30.7, 25.8, 25.2, 22.3, 19.6, 13.8, 10.0. ESMS *m*/*z*: 514.1 (M + 1). Anal. ($C_{27}H_{29}Cl_2N_3OS$) C, H, N.

**1-(2,4-Dichlorophenyl)-5-(5-(3,3-dimethylbut-1-ynyl)thiophen-2-yl)-4-methyl-*N*-(piperidin-1-yl)-1*H*-pyrazole-3-carboxamide (34).** Starting from carboxylic acid **11e** (108 mg, 0.25 mmol), compound **34** was synthesized following a similar coupling procedure for **12** and obtained as a white solid (94 mg, 73%): mp 166−167 °C; $^1$H NMR ($CDCl_3$) $\delta$ 7.63 (s, 1H), 7.43 (s, 1H), 7.30−7.26 (m, 2H), 6.91 (d, $J$ = 3.6 Hz, 1H), 6.62 (d, $J$ = 3.6 Hz, 1H), 2.84−2.74 (m, 4H), 2.40 (s, 3H), 1.70−1.62 (m, 4H), 1.40−1.32 (m, 2H), 1.23 (s, 9H); $^{13}$C NMR ($CDCl_3$) $\delta$ 159.6, 144.1, 137.2, 136.2, 135.6, 133.5, 130.8, 130.6, 130.1, 128.3, 128.1, 127.8, 126.4, 119.0, 104.2, 71.3, 56.8, 30.5, 29.5, 25.2, 23.1, 9.5. ESMS *m*/*z*: 515.1 (M + 1). Anal. ($C_{26}H_{28}Cl_2N_4OS$) C, H, N.

**1-(2,4-Dichlorophenyl)-5-(5-(3,3-dimethylbut-1-ynyl)thiophen-2-yl)-*N*-(hexahydrocyclopenta[*c*]pyrrol-2(1*H*)-yl)-4-methyl-1*H*-pyrazole-3-carboxamide (35).** Starting from carboxylic acid **11e** (108 mg, 0.25 mmol), compound **35** was synthesized following a similar coupling procedure for **13** and obtained as a white solid (96 mg,

71%): mp 170.5−171 °C; $^1$H NMR ($CDCl_3$) $\delta$ 7.54 (s, 1H), 7.47 (s, 1H), 7.34−7.30 (m, 2H), 6.96 (d, $J$ = 3.6 Hz, 1H), 6.67 (d, $J$ = 3.6 Hz, 1H), 3.30−3.21 (m, 2H), 2.70−2.60 (m, 2H), 2.46 (s, 3H), 1.68−1.52 (m, 6H), 1.30−1.25 (m, 2H), 1.27 (s, 9H); $^{13}$C NMR ($CDCl_3$) $\delta$ 160.3, 144.1, 137.2, 136.2, 135.6, 133.5, 130.9, 130.6, 130.1, 128.3, 128.1, 127.8, 126.4, 119.0, 104.2, 71.3, 62.4, 40.3, 32.1, 30.5, 29.5, 25.5, 9.5. ESMS *m*/*z*: 541.1 (M + 1). Anal. ($C_{28}H_{30}Cl_2N_4OS$) C, H, N.

**5-(5-(Cyclopropylethynyl)thiophen-2-yl)-1-(2,4-dichlorophenyl)-4-methyl-*N*-(piperidin-1-yl)-1*H*-pyrazole-3-carboxamide (36).** Starting from the carboxylic acid **11f** (104 mg, 0.25 mmol), compound **36** was synthesized following a similar coupling procedure for **12** and obtained as a white solid (90 mg, 72%): mp 176−177 °C; $^1$H NMR ($CDCl_3$) $\delta$ 7.59 (s, 1H), 7.49 (d, $J$ = 1.5 Hz, 1H), 7.30−7.26 (m, 2H), 6.95 (d, $J$ = 3.6 Hz, 1H), 6.68 (d, $J$ = 3.6 Hz, 1H), 3.26 (t, $J$ = 4.5 Hz, 4H), 2.46 (s, 3H), 1.80−1.65 (m, 4H), 1.50−1.38 (m, 3H), 0.91−0.78 (m, 4H); $^{13}$C NMR ($CDCl_3$) $\delta$ 159.7, 144.3, 137.3, 136.3, 135.7, 133.7, 131.2, 130.7, 130.2, 128.6, 128.2, 127.9, 126.5, 119.2, 99.7, 68.0, 57.0, 25.3, 23.3, 9.6, 8.8, 0.3. ESMS *m*/*z*: 499.2 (M + 1). Anal. ($C_{25}H_{24}Cl_2N_4OS$) C, H, N.

**5-(5-(Cyclopropylethynyl)thiophen-2-yl)-1-(2,4-dichlorophenyl)-*N*-(hexahydrocyclopenta[*c*]pyrrol-2(1*H*)-yl)-4-methyl-1*H*-pyrazole-3-carboxamide (37).** Starting from carboxylic acid **11f** (104 mg, 0.25 mmol), compound **37** was synthesized following a similar coupling procedure for **13** and obtained as a white solid (95 mg, 72%): mp 104−105 °C; $^1$H NMR ($CDCl_3$) $\delta$ 7.48 (d, $J$ = 1.8 Hz, 1H), 7.42−7.28 (m, 2H), 6.95 (d, $J$ = 3.6 Hz, 1H), 6.68 (d, $J$ = 3.6 Hz, 1H), 3.26 (t, $J$ = 7.8 Hz, 2H), 2.54−2.42 (m, 2H), 2.46 (s, 3H), 1.70−1.20 (m, 9H), 0.96−0.78 (m, 4H); $^{13}$C NMR ($CDCl_3$) $\delta$ 160.4, 144.2, 137.3, 136.3, 135.8, 133.7, 131.1, 130.7, 130.2, 128.6, 128.1, 127.9, 126.5, 119.1, 99.7, 68.0, 62.5, 40.4, 32.3, 25.6, 9.6, 8.7, 0.3. ESMS *m*/*z*: 525.2 (M + 1). Anal. ($C_{27}H_{26}Cl_2N_4OS$) C, H, N.

**5-(5-(Cyclopentylethynyl)thiophen-2-yl)-1-(2,4-dichlorophenyl)-4-methyl-*N*-(piperidin-1-yl)-1*H*-pyrazole-3-carboxamide (38).** Starting from carboxylic acid **11g** (111 mg, 0.25 mmol), compound **38** was synthesized following a similar coupling procedure for **12** and obtained as a white solid (93 mg, 72%): mp 133−134 °C; $^1$H NMR ($CDCl_3$) $\delta$ 7.60 (s, 1H), 7.49 (s, 1H), 7.40−7.34 (m, 2H), 6.96 (d, $J$ = 3.6 Hz, 1H), 6.68 (d, $J$ = 3.6 Hz, 1H), 2.92−3.76 (m, 5H), 2.46 (s, 3H), 2.02−1.82 (m, 2H), 1.81−1.50 (m, 10H), 1.45−1.25 (m, 2H); $^{13}$C NMR ($CDCl_3$) $\delta$ 159.3, 143.9, 137.0, 136.0, 135.4, 133.2, 130.5, 129.8, 128.1, 127.9, 127.6, 126.4, 118.7, 100.4, 72.1, 56.6, 33.2, 30.5, 25.0, 24.7, 23.0, 9.2. ESMS *m*/*z*: 527.3 (M + 1). Anal. ($C_{27}H_{28}Cl_2N_4OS$) C, H, N.

**5-(5-(Cyclopentylethynyl)thiophen-2-yl)-1-(2,4-dichlorophenyl)-*N*-(hexahydrocyclopenta[*c*]pyrrol-2(1*H*)-yl)-4-methyl-1*H*-pyrazole-3-carboxamide (39).** Starting from carboxylic acid **11g** (111 mg, 0.25 mmol), compound **39** was synthesized following a similar coupling procedure for **13** and obtained as a white solid (97 mg, 70%): mp 170−171 °C; $^1$H NMR ($CDCl_3$) $\delta$ 7.48 (d, $J$ = 1.8 Hz, 1H), 7.38−7.33 (m, 2H), 6.95 (d, $J$ = 3.9 Hz, 1H), 6.67 (d, $J$ = 3.9 Hz, 1H), 3.26 (t, $J$ = 7.8 Hz, 2H), 2.80 (q, $J$ = 7.2 Hz, 1H), 2.58−2.42 (m, 2H), 2.46 (s, 3H), 2.02−1.84 (m, 2H), 1.81−1.40 (m, 12H), 1.28−1.22 (m, 2H); $^{13}$C NMR ($CDCl_3$) $\delta$ 160.4, 144.2, 137.3, 136.3, 135.7, 133.6, 130.8, 130.7, 130.2, 128.4, 128.1, 127.8, 126.6, 119.0, 100.7, 72.3, 62.4, 40.4, 33.5, 32.2, 30.8, 25.5, 25.0, 9.5. ESMS *m*/*z*: 553.2 (M + 1). Anal. ($C_{29}H_{30}Cl_2N_4OS$) C, H, N.

**5-(5-(Cyclohexylethynyl)thiophen-2-yl)-1-(2,4-dichlorophenyl)-4-methyl-*N*-(piperidin-1-yl)-1*H*-pyrazole-3-carboxamide (40).** Starting from carboxylic acid **11h** (115 mg, 0.25 mmol), compound **40** was synthesized following a similar coupling procedure for **12** and obtained as a white solid (97 mg, 72%): mp 115−116 °C; $^1$H NMR ($CDCl_3$) $\delta$ 7.61 (s, 1H), 7.44 (s, 1H), 7.36−7.30 (m, 2H), 6.92 (d, $J$ = 3.6 Hz, 1H), 6.63 (d, $J$ = 3.6 Hz, 1H), 2.86−2.72 (m, 4H), 2.60−2.48 (m, 1H), 2.47 (s, 3H), 1.82−1.60 (m, 8H), 1.56−1.20 (m, 8H); $^{13}$C NMR ($CDCl_3$) $\delta$ 159.6, 144.2, 137.2, 136.2, 135.7, 133.5, 130.8, 130.7, 130.1, 128.3, 128.1, 127.8, 126.5, 119.1, 100.4, 72.7, 56.9, 32.2, 29.5, 25.6, 25.3, 24.7, 23.2, 9.5. ESMS *m*/*z*: 541.1 (M + 1). Anal. ($C_{28}H_{30}Cl_2N_4OS$) C, H, N.

**5-(5-(Cyclohexylethynyl)thiophen-2-yl)-1-(2,4-dichlorophenyl)-*N*-(hexahydrocyclopenta[*c*]pyrrol-2(1*H*)-yl)-4-methyl-1*H*-pyrazole-3-carboxamide (41).** Starting from carboxylic acid **11h** (115 mg, 0.25 mmol), compound **41** was synthesized following a similar coupling procedure for **13** and obtained as a white solid (99 mg, 70%): mp 169−169.5 °C; $^1$H NMR ($CDCl_3$) $\delta$ 7.49 (d, $J$ = 2.0 Hz, 1H), 7.36−7.30 (m, 2H), 6.96 (d, $J$ = 4.0 Hz, 1H), 6.67 (d, $J$ = 4.0 Hz, 1H), 3.27 (t, $J$ = 8.0 Hz, 2H), 2.60−2.48 (m, 3H), 2.47 (s, 3H), 1.92−1.20 (m, 18H); $^{13}$C NMR ($CDCl_3$) $\delta$ 160.5, 144.2, 137.4, 136.4, 135.8, 133.7, 131.0, 130.8, 130.3, 128.5, 128.2, 127.9, 126.7, 119.2, 100.6, 72.8, 62.5, 40.4, 32.3, 29.9, 29.7, 25.7, 25.6, 24.9, 9.6. ESMS *m*/*z*: 567.1 (M + 1). Anal. ($C_{30}H_{32}Cl_2N_4OS$) C, H, N.

**General Synthetic Procedure for the Preparation of Compounds 42−48.** The general procedure is illustrated immediately below with compound **42** as a specific example.

**1-(2,4-Dichlorophenyl)-4-methyl-5-(5-(4-phenylbut-1-ynyl)thiophen-2-yl)-*N*-(piperidin-1-yl)-1*H*-pyrazole-3-carboxamide (42).** To a solution of bromothiophene **6** (0.26 g, 0.50 mmol), $PdCl_2(PPh_3)_2$ (35 mg, 0.05 mmol), and CuI (7 mg, 0.03 mmol) in THF (4 mL) was added but-3-ynylbenzene (144 mg, 1.11 mmol) and 0.5 M aqueous solution of 2-ethanolamine (3 mL). The resulting mixture was heated at 60 °C for 6 h. After cooling to room temperature, the reaction mixture was poured into the 10 mL of water and extracted with (2 × 10 mL) of diethyl ether. The combined extracts were washed with water and brine, dried over anhydrous sodium sulfate, filtered, and evaporated. The resulting residue was purified by flash column chromatography with *n*-hexane/ethyl acetate (5:1) to afford compound **42** (0.27 g, 95%) as a white solid: mp 82−83 °C; $^1$H NMR ($CDCl_3$) $\delta$ 7.67 (s, 1H), 7.45 (s, 1H), 7.34−7.18 (m, 7H), 6.94 (d, $J$ = 3.6 Hz, 1H), 6.74 (d, $J$ = 3.6 Hz, 1H), 2.90−2.80 (m, 6H), 2.65 (t, $J$ = 7.2 Hz, 2H), 2.46 (s, 3H), 1.78−1.64 (m, 4H), 1.46−1.32 (m, 2H); $^{13}$C NMR ($CDCl_3$) $\delta$ 159.5, 144.1, 139.9, 137.0, 136.2, 135.5, 133.4, 130.8, 130.6, 129.9, 128.5, 128.1, 127.9, 127.7, 126.2, 126.0, 118.9, 95.6, 73.5, 56.7, 34.5, 25.1, 23.1, 21.7, 9.4. ESMS *m*/*z*: 563.1 (M + 1). Anal. ($C_{30}H_{28}Cl_2N_4OS$) Calcd: C 63.94; H 5.01; N 9.94. Found: C 63.38; H 4.75; N 9.86.

**1-(2,4-Dichlorophenyl)-5-(5-(3-methoxyprop-1-ynyl)thiophen-2-yl)-4-methyl-*N*-(piperidin-1-yl)-1*H*-pyrazole-3-carboxamide (43).** Sequential treatment of a mixture of bromothiophene **6** (0.26 g, 0.50 mmol), $PdCl_2(PPh_3)_2$ (35 mg, 0.05 mmol), and CuI (6 mg, 0.03 mmol) in THF (3 mL) with 3-methoxyprop-1-yne (80 mg, 1.15 mmol) and 2-ethanolamine (0.5 M (aqueous), 3 mL) for 6 h gave compound **43** (0.24 g, 92%) as a pale-yellow oil. $^1$H NMR ($CDCl_3$) $\delta$ 7.62 (s, 1H), 7.49 (d, $J$ = 1.2 Hz, 1H), 7.35−7.34 (m, 2H), 7.08 (d, $J$ = 3.6 Hz, 1H), 6.74 (d, $J$ = 3.6 Hz, 1H), 4.30 (s, 2H), 3.41 (s, 3H), 2.84 (t, $J$ = 4.8 Hz, 4H), 2.48 (s, 3H), 1.78−1.71 (m, 4H), 1.46−1.42 (m, 2H); $^{13}$C NMR ($CDCl_3$) $\delta$ 159.6, 144.2, 137.0, 136.4, 135.5, 133.6, 132.3, 130.7, 130.2, 130.0, 128.1, 127.9, 124.7, 119.3, 91.8, 78.2, 60.3, 57.8, 57.0, 25.3, 23.2, 9.5. ESMS *m*/*z*: 503.1 (M + 1). Anal. ($C_{24}H_{24}Cl_2N_4O_2S$) Calcd: C 57.26; H 4.81; N 11.13. Found: C 57.06; H 5.19; N 10.63.

**3-(2,4-Dichlorophenyl)-4-(5-(3-ethoxyprop-1-ynyl)thiophen-2-yl)-5-methyl-*N*-(piperidin-1-yl)cyclopenta-1,4-dienecarboxamide (44).** Sequential treatment of a mixture of bromothiophene **6** (0.26 g, 0.50 mmol), $PdCl_2(PPh_3)_2$ (35 mg, 0.05 mmol), and CuI (6 mg, 0.03 mmol) in THF (3 mL) with 3-ethoxyprop-1-yne (98 mg, 1.15 mmol) and 2-ethanolamine (0.5 M (aqueous), 3 mL) for 7 h afforded compound **44** (0.24 g, 92%) as a pale-yellow oil. $^1$H NMR ($CDCl_3$) $\delta$ 7.59 (s, 1H), 7.49 (d, $J$ = 1.2 Hz, 1H), 7.35−7.34 (m, 2H), 7.07 (d, $J$ = 3.9 Hz, 1H), 6.73 (d, $J$ = 3.9 Hz, 1H), 4.34 (s, 2H), 3.60 (q, $J$ = 7.1 Hz, 1H), 2.84 (t, $J$ = 4.8 Hz, 4H), 2.47 (s, 3H), 1.78−1.71 (m, 4H), 1.46−1.42 (m, 2H), 1.24 (t, $J$ = 6.9 Hz, 6H); $^{13}$C NMR ($CDCl_3$) $\delta$ 159.6, 144.3, 137.0, 136.4, 135.6, 133.6, 132.2, 130.7, 130.2, 130.0, 128.1, 127.9, 124.7, 119.3, 91.3, 78.2, 65.7, 58.4, 57.0, 25.3, 23.2, 14.9, 9.5. ESMS *m*/*z*: 517.1 (M + 1). Anal. ($C_{25}H_{26}Cl_2N_4O_2S$) Calcd: C 58.03; H 5.06; N 10.83. Found: C 57.55; H 5.37; N 10.63.

**1-(2,4-Dichlorophenyl)-5-(5-(3-isopropoxyprop-1-ynyl)thiophen-2-yl)-4-methyl-*N*-(piperidin-1-yl)-1*H*-pyrazole-3-carboxamide (45).** Sequential treatment of a mixture of bromothiophene **6** (0.26 g, 0.50 mmol), $PdCl_2(PPh_3)_2$ (35 mg, 0.05 mmol), and CuI (6 mg, 0.03 mmol) in THF (3 mL) with 3-isopropoxyprop-1-yne (110 mg, 1.12 mmol) and 2-ethanolamine (0.5 M (aqueous), 3 mL) for 6.5 h gave compound **45** (0.24 g, 94%) as a pale-yellow oil. $^1$H NMR ($CDCl_3$) $\delta$ 7.60 (s, 1H), 7.49 (d, $J$ = 1.5 Hz, 1H), 7.38−7.31 (m, 2H), 7.07 (d, $J$ = 3.9 Hz, 1H), 6.73 (d, $J$ = 3.9 Hz, 1H), 4.34 (s, 2H), 3.80 (septet, $J$ = 6.3 Hz, 1H), 2.84 (t, $J$ = 5.1 Hz, 4H), 2.47 (s, 3H), 1.78−1.71 (m, 4H), 1.42−1.25 (m, 2H), 1.20 (d, $J$ = 6.3 Hz, 6H); $^{13}$C NMR ($CDCl_3$) $\delta$ 159.7, 144.3, 137.1, 136.5, 135.6, 133.7, 132.2, 130.7, 130.3, 130.0, 128.2, 127.9, 124.9, 119.3, 91.7, 71.0, 57.0, 56.0, 29.6, 25.3, 23.3, 21.8, 9.6. ESMS *m*/*z*: 531.1 (M + 1). Anal. ($C_{26}H_{28}Cl_2N_4O_2S$) C, H, N.

**1-(2,4-Dichlorophenyl)-5-(5-(3-(isopropylamino)prop-1-ynyl)-thiophen-2-yl)-4-methyl-*N*-(piperidin-1-yl)-1*H*-pyrazole-3-carboxamide (46).** Sequential treatment of a mixture of bromothiophene **6** (0.25 g, 0.50 mmol), $PdCl_2(PPh_3)_2$ (35 mg, 0.05 mmol), and CuI (6 mg, 0.03 mmol) in THF (4 mL) with *N*-isopropylprop-2-yn-1-amine (99 mg, 1.02 mmol) and 2-ethanolamine (0.5 M (aqueous), 3 mL) for 8 h gave product **46** (0.26 g, 93%) as a pale-yellow oil. $^1$H NMR ($CDCl_3$) $\delta$ 7.62−7.58 (m, 1H), 7.48−7.40 (m, 2H), 6.97 (d, $J$ = 3.6 Hz, 1H), 6.67 (d, $J$ = 3.6 Hz, 1H), 3.58 (s, 2H), 2.96 (septet, $J$ = 6.4 Hz, 1H), 2.82−2.76 (m, 4H), 2.42 (s, 3H), 1.76−1.64 (m, 4H), 1.40−1.30 (m, 2H), 1.01 (d, $J$ = 6.4 Hz, 6H); $^{13}$C NMR ($CDCl_3$) $\delta$ 159.6, 144.2, 137.0, 136.3, 135.6, 132.0, 131.8, 131.7, 130.7, 130.1, 128.3, 128.0, 125.4, 119.1, 93.9, 75.4, 58.9, 47.0, 36.5, 25.2, 23.2, 22.4, 9.4. ESMS *m*/*z*: 530.1 (M + 1). Owing to its hygroscopic and unstable properties, the purity of compound **46** was determined by Hitachi diode array detector L-2455 and pump L-2130 HPLC system. HPLC retention times were reported using Waters XTerra RP1835 $\mu$M 4.6 mm× 100 mm column with elution conditions MeCN−$H_2O$ (40:60). The flow rate is 0.5 mL/min and the injection volume is 10 $\mu$L. The system was operated at 25 °C. Peaks were detected at 240−260 nm; $t_R$ = 10.18 min; purity = 95.13%.

**1-(2,4-Dichlorophenyl)-5-(5-(3-(dimethylamino)prop-1-ynyl)-thiophen-2-yl)-4-methyl-*N*-(piperidin-1-yl)-1*H*-pyrazole-3-carboxamide (47).** Sequential treatment of a mixture of bromothiophene **6** (0.26 g, 0.50 mmol), $PdCl_2(PPh_3)_2$ (35 mg, 0.05 mmol), and CuI (7 mg, 0.03 mmol) in THF (4 mL) with *N*,*N*-dimethylprop-2-yn-1-amine (88 mg, 1.06 mmol) and 2-ethanolamine (0.5 M (aqueous), 3 mL) for 7.5 h afforded compound **47** (0.24 g, 92%) as a white solid: mp 85−86.5 °C; $^1$H NMR ($CDCl_3$) $\delta$ 7.60 (s, 1H), 7.50 (d, $J$ = 2.0 Hz, 1H), 7.36−7.30 (m, 2H), 7.04 (d, $J$ = 3.6 Hz, 1H), 6.71 (d, $J$ = 3.6 Hz, 1H), 3.45 (s, 2H), 2.90−2.80 (m, 4H), 2.48 (s, 3H), 2.33 (s, 6H), 1.80−1.68 (m, 4H), 1.50−1.40 (m, 2H); $^{13}$C NMR ($CDCl_3$) $\delta$ 159.7, 144.3, 137.2, 136.5, 135.7, 133.7, 131.8, 130.8, 130.3, 129.4, 128.2, 127.9, 125.5, 119.3, 90.9, 77.5, 57.1, 48.7, 44.3, 25.4, 23.3, 9.6. ESMS *m*/*z*: 516.1 (M + 1). Anal. ($C_{25}H_{27}Cl_2N_5OS$) Calcd: C 58.14; H 5.27; N 13.56. Found: C 58.58; H 5.55; N 12.97.

**1-(2,4-Dichlorophenyl)-4-methyl-5-[5-(3-phenoxyprop-1-ynyl)-thiophen-2-yl]-1*H*-pyrazole-3-carboxylic Acid Piperidin-1-ylamide (48).** Sequential treatment of a mixture of bromothiophene **6** (0.26 g, 0.5 mmol), $PdCl_2(PPh_3)_2$ (35 mg, 0.05 mmol), and CuI (6 mg, 0.03 mmol) in THF (3 mL) with phenyl propargyl ether (132 mg, 1.0 mmol) and 2-ethanolamine (0.5 M (aqueous), 3 mL) for 8 h furnished product **48** (0.26 g, 92%) as a pale-yellow oil. $^1$H NMR ($CDCl_3$) $\delta$ 7.58 (s, 1H), 7.49 (d, $J$ = 1.8 Hz, 2H), 7.35−7.28 (m, 4H), 7.08 (d, $J$ = 3.6 Hz, 1H), 7.03−6.97 (m, 3H), 6.72 (d, $J$ = 3.6 Hz, 1H), 4.89 (s, 2H), 2.84 (t, $J$ = 4.8 Hz, 4H), 2.47 (s, 3H), 1.76−1.71 (m, 4H), 1.43−1.25 (m, 2H); $^{13}$C NMR ($CDCl_3$) $\delta$ 159.6, 157.5, 144.3, 136.5, 135.6, 133.7, 132.7, 130.7, 130.5, 130.3, 129.5, 128.2, 128.0, 124.3, 121.5, 119.4, 114.8, 89.7, 79.5, 57.1, 56.4, 25.3, 23.3, 9.6. ESMS *m*/*z*: 565.1 (M + 1). Anal. ($C_{29}H_{26}Cl_2N_4O_2S$) C, H, N.

**B. Biological Evaluation.** The following test methods were used to generate the data in Tables 1−3 and Figures 2−4.

**B1. Establishment of Human CB1 (hCB1) and CB2 (hCB2) Stable Cell Lines and Membrane Purification.** The hCB1 cDNA tagged with Flag at the N terminus or hCB2 cDNA was subcloned into the pIRES2-EGFP vector (Clontech Laboratories, Inc., Mountain View, CA). After transfection to HEK 293 cells, clones stably expressed either hCB1 or hCB2 were selected by GFP and G418 sulfate and maintained in DMEM supplemented with 10% fetal bovine serum and 0.5 mg/mL G418 sulfate under 5% $CO_2$ at 37 °C. For membrane purification, cells were homogenized in ice-cold buffer A (50 mM Tris, 5 mM $MgCl_2$, 2.5 mM EDTA, pH 7.4, 10% sucrose) with 1 mM PMSF. The homogenate was centrifuged for 15 min at 2000*g* at 4 °C. The resulting supernatant was centrifuged for another 30 min at 43000*g* at 4 °C. The final pellet was resuspended in buffer A and stored at −80 °C.

**B2. Radioligand Binding Assay.**[34] The radioligand binding assay was performed according to Felder et al.[34] with minor modification. An amount of 0.2−8 $\mu$g of the purified membrane was incubated with 0.75 nM [$^3$H]-**49** (see footnote a in Table 1) and compounds of interest in the incubation buffer (50 mM Tris-HCl, 5 mM $MgCl_2$, 1 mM EDTA, 0.3% BSA, pH 7.4). The nonspecific binding was defined in the presence of 1 $\mu$M **49**. The reactions were incubated for 1.5 h at 30 °C in MultiScreen microplates (Millipore Corp., Billerica, MA). The reactions were terminated by manifold filtration and washed with ice-cold wash buffer (50 mM Tris, pH 7.4, 0.25% BSA) four times. The radioactivity bound to the filters was measured by Topcount (Perkin Elmer Inc., Waltham, MA). $IC_{50}$ was determined by the concentration of compounds required to inhibit 50% of the binding of [$^3$H]-**49** and calculated by nonlinear regression (GraphPad software, San Diego, CA).

**B3. Eu-GTP Binding Assay.**[35,36] The Eu-GTP binding assay was performed using the DELFIA Eu-GTP binding kit (Perkin-Elmer Inc., Waltham, MA) based on methods developed by Frang et al.[35] with minor modifications as described in the following: 1−4 $\mu$g of purified membrane was incubated with compounds of interest and 20 nM **49** (see footnote a in Table 1) in assay buffer (50 mM HEPES, pH 7.4, 100 mM NaCl, 100 $\mu$g/mL saponin, 5 mM $MgCl_2$, 2 $\mu$M GDP, 0.5% BSA) at 30 °C for 60 min in acroplates (Pall Life Sciences, Ann Arbor, MI). Following the addition of Eu-GTP and incubation of 30 min at 30 °C, the assay was terminated by washing four times in washing buffer provided in the kit. The fluorescence signal of Eu-GTP was determined by Victor 2 multilabel reader (Perkin Elmer Inc., Waltham, MA). $EC_{50}$ values were analyzed by increasing concentrations of test compounds after activation with 30 nM of **49** and were determined by nonlinear regression analysis using the GraphPad Prism program (GraphPad Software, San Diego, CA). For determination of intrinsic property of test compounds, percentage change compared to the basal level is defined as [(Eu-GTP binding in the presence of test compound at 10 $\mu$M-basal Eu-GTP binding)/basal Eu-GTP binding] × 100%. As demonstrated with representative compounds **12** and **14**, **15** and **16**, and **18** and **19**, a typical graph defining three different intrinsic properties, including NA, PA and IA, is illustrated below (Figure 4).

**B4. Spontaneously Feeding Model.**[7] Male Wistar rats were individually housed under 12 h reverse light−dark cycle (light off at 10 a.m.) for more than a week and weighed 210−270 g at the start of the study. Drugs at defined dosage or vehicle (20% DMSO/10% Tween-80/70% $H_2O$)[37] were orally gavaged before the light off, and sufficient powder chow diet was supplied at 11 a.m. The unconsumed food was measured after 1, 2, 3, and 6 h. Food intake was expressed as calorie (cal) normalized by body weight (g).

**B5. DIO Mouse Model.**[8] Six-week-old C57BL/6 mice were given high-fat diet of 4.7 kcal/g energy density (Harlan TD 97366; 49% fat, 18% protein, and 33% carbonhydrate) for 16−22 weeks before the drug treatment. Mice weight matched were assigned to different groups and orally gavaged daily with vehicle (10% DMSO/10% Tween-80/70% $H_2O$)[37] or compounds at defined dosage for 21 days. The sum of food taken for each treatment and body weight was measured daily.

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**Supporting Information Available:** Combustion analysis data for compounds **4**−**7**, **11**, **11a**,**c**,**d**,**f**,**g**, **12**−**45**, **47**, and **48**; HPLC purity analysis of compound **46**. This material is available free of charge via the Internet at http://pubs.acs.org.

## References

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