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PAPER

Metal-free synthesis of 3,5-disubstituted 1*H*- and 1-aryl-1*H*-pyrazoles from 1,3-diyne-indole derivatives employing two successive hydroaminations

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A robust and efficient atom-economic one-pot synthesis of 3,5-disubstituted 1*H*- and 1-aryl-1*H*-pyrazoles under base, acid and metal-free reaction conditions, is reported. The transformation conveniently takes place between 1,4-disubstituted 1,3-diynes and hydrazines in PEG-400 as an eco-friendly solvent, and involves two successive hydroaminations. The reaction was optimized for both, symmetric and non- symmetric 1,3-diyne-indole derivatives, as well as for hydrazine and substituted phenylhydrazines. The scope and limitatons of the transformation were examined, observing that it is not sensitive to moisture or atmospheric oxygen, and that it tolerates a variety of functional groups. Even sterically hindered substrates afforded the expected pyrazoles in good to excellent yields, under mild conditions. A detailed reaction mechanism, which explains its regioselectivity, was also proposed.

Introduction

The pyrazoles are a large and well-known class of five-membered ring heterocycles with two adjacent nitrogen atoms, which have captured great scientific interest. This is because many pyrazole derivatives possess relevant physiological activity,[1] being useful as pharmaceuticals,[2] agrochemicals, pesticides and crop protecting agents.[3] Celecoxib,[4] Mavacoxib, Rimonabant, Mepiprazole, Lonazolac and Zoniporide (Figure 1) illustrate their participation as members of the current pharmaceutical arsenal, whereas Fenpyroximate, RPA 406194, Tebufenpyrad and Cyenopyrafen[5] are representative examples of agrochemicals and biocides with a pyrazole ring as a key framework.

The pyrazoles are also useful in organic chemistry, as synthetic building blocks, being employed as versatile, pluripotent ligands in coordination chemistry[6] and for transition metal cross-coupling and polymerization reactions.[7] In addition, these heterocycles have aroused high interest for their uses with technological impact, as ultraviolet stabilizers, photoprotecting agents, energetic materials and many other applications.[8] Interestingly, however, despite there are natural products carrying the pyrazole ring system, these heterocycles are not widespread in Nature.[9]

Methods for accessing the pyrazole ring system[10] involve mainly the [3+2] cycloaddition of 1,3-dielectrophiles with hydrazine or substituted hydrazines. Suitable 1,3-dielectrophiles

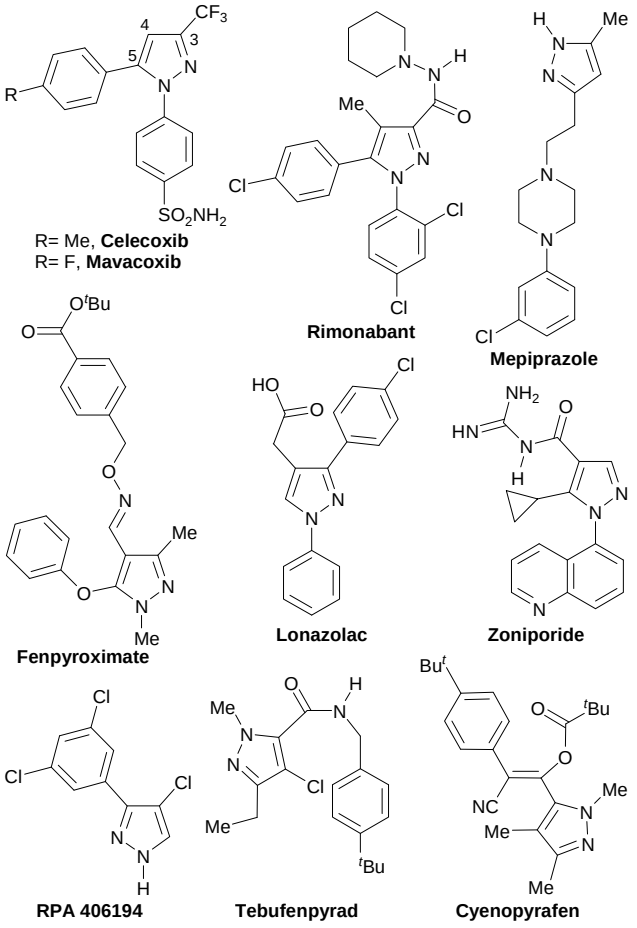

Figure 1. Selected polysubstituted pyrazoles of biological interest.

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employed include 1,3-diketones (Knorr reaction) and their derivatives,[11] α,β-unsaturated aldehydes and ketones,[12] allenic ketones,[13a,b] ene-ynes,[13c] and β-alkynyl ketones.[14] Preformed α-alkynyl (propargylic) hydrazones have also been used.[15]

Practically all linear 1,3-diketones undergo the Knorr reaction to afford the corresponding pyrazole derivatives upon reaction with hydrazines.[16] Additional alternatives include the 1,3-dipolar cycloadditions of nitrile imines or diazo compounds with α-methylene carbonyls, alkynes,[17] and others.[18]

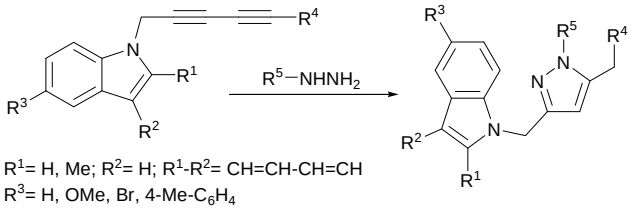
In general, these methods have both, advantages and disadvantages; the latter include the use of expensive catalysts, and reagents or starting materials which are toxic, explosive or difficult to prepare and handle.[19] Functional group incompatibilities or substrate limitations, and the formation of appreciable amounts of undesired isomers are additional, but still relevant, drawbacks.[20] Therefore, the exploration of new approaches toward pyrazoles is always of interest.

On the other side, the indole moiety is a privileged scaffold. The heterocycle is an integral part of a wide array of natural products and bioactive compounds, including many entities of therapeutic importance. The synthesis of functionalized indoles and complex indole derivatives has been an active focus of research over the years.

Because of the ubiquity of both, indoles and pyrazoles, among biologically active compounds, there is a constant striving to develop new methods for their synthesis. The combination of the indole nucleus with the pyrazole skeleton has attracted some interest,[21] on the basis that it may result in compounds with enhanced bioactivity.[22] Bioactive compounds carrying both heterocyclic nuclei have been reported;[23] furthermore, indoles carrying pyrazole derivatives attached through the indolic nitrogen have been patented as inhibitors of the binding of ^{3}H-vasopressin to the human vasopressin V1a receptor.[24]

Many protocols toward pyrazoles require either precious metals, expensive ligands, extensive heating, have a limited scope or afford unacceptable mixtures of isomers.[25] Surprisingly, however, the synthesis of polysubstituted pyrazoles from 1,3-diynes has been scarcely explored.[26] The 1,3-diyne motif, a chemical entity prone to be involved in cyclization reactions, is a synthetic equivalent of the 1,3-diketone framework and of some other functionalized carbonyl or alkyne precursors of pyrazoles.[27]

Therefore, taking into account our recently described access to 1,2-isoxazoles from 1,3-diynes in PEG-400, promoted by Et_3N,[28] and in continuation of our research efforts toward the synthesis of polysubstituted heterocyclic compounds under efficient and eco-friendly conditions,[29] here we wish to report a rapid and efficient one-pot and metal-free synthesis of 3,5-disubstituted 1*H*- and 1-aryl-1*H*- pyrazoles from 1,4-disubstituted 1,3-diynes (Scheme 1).



R^1= H, Me; R^2= H; R^1-R^2= CH=CH-CH=CH
R^3= H, OMe, Br, 4-Me-C_6H_4
R^4= Ph, 4-Me-C_6H_4, CH_2*N*-Carbazolyl, CH_2*N*-indolyl (R^1,R^2,R^3-substituted)
R^5= H, 4-Br-C_6H_4, 4-Cl-C_6H_4,4-Me-C_6H_4

Scheme 1. Proposed approach toward indole-derived 1*H*- and 1-aryl-1*H*-3,5-disubstituted pyrazoles.

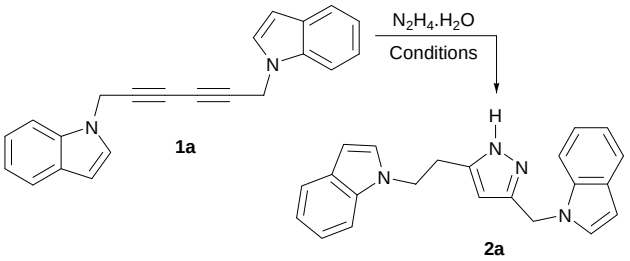
The process, which is also robust, being resistant to oxygen and moisture, entails two successive and atom-economic hydroaminations of symmetric and non-symmetric 1,3-diyne derivatives of indoles, with hydrazine and arylhydrazines as dinucleophiles.

Results and discussion

In order to optimize the conditions for the transformation, the reaction of hydrazine hydrate (24% in H_2O, 0.9 mmol) was initially tested with 1,6-di-(1*H*-indol-1-yl)hexa-2,4-diyne (**1a**, 0.3 mmol) as starting material,[28] achieving the results summarized in Table 1.

Following a protocol reminiscent of that disclosed by Bao *et al.*,[26a,b] with DMSO as solvent (0.5 mL), it was observed that the reaction was completed after 3 h at 60ºC, furnishing 74% of the expected product **2a** (entry 1). Increasing the temperature to 80ºC and 100ºC shortened the reaction time to 1 h and improved the yields to 79% and 83%, respectively (entries 2 and 3). Interestingly, these initial yields were comparatively better than than those reported by Bao for an analogous transformation and can be adscribed to the assistance of the indolic nitrogen.

Table 1. Optimization of the reaction conditions for the synthesis of the 3,5-disubstituted 1*H*-pyrazole **2a**.[a]



Entry Nº	Solvent	$N_2H_4.H_2O$ (equiv.)	Temp. (°C)	Time (h)	Yield (%)
1	DMSO	3.0	60	3	74
2	DMSO	3.0	80	1	79
3	DMSO	3.0	100	1	83
4	EtOH	3.0	Reflux	24	73
5	MeOH	3.0	Reflux	24	31
6	2-PrOH	3.0	Reflux	24	70
7	PEG-400	3.0	100	1	90
8	PEG-400	3.0	120	1	84
9	PEG-400	3.0	80	3	75
10	PEG-400	2.0	100	1	89
11	PEG-400	1.5	100	1	80
12[b]	PEG-400	2.0	100	1	78

[a] Reaction conditions: Diyne (**1a**, 0.3 mmol); Solvent (0.5 mL).

[b] The reaction was performed under microwave irradiation.

After these initial trials and with the goal of employing more sustainable solvents, the use of low molecular weight alcohols (MeOH, EtOH, 2-PrOH) and PEG-400 was tested. Unfortunately, the former required too long reaction times (24 h), despite employing reflux conditions (entries 4-6), whereas, in addition, MeOH afforded a disappointingly low yield (31%) of product (entry 5).

On the contrary, the use of PEG-400 appeared as a substantial improvement, affording 90% **2a** after heating only 1 h at 100ºC (entry 7). Therefore, the influence of the temperature on the outcome of the reaction in PEG-400 was examined at 120 and

80ºC. However, under these conditions only lower yields were observed (entries 8 and 9); furthermore, at 80ºC, the reaction took 3 hours to afford 75% of **2a** (entry 9).

Next, the effect of the quantity of hydrazine was screened at 100ºC. The experiments revealed that lowering its amount to 2.0 equivalents had little or no effect on the reaction outcome, affording 89% yield of **2a** (entry 10); however, a further reduction to 1.5 equivalents H_2NNH_2 resulted in 80% **2a**, a substantially diminished performance (entry 11).

A final test was conducted under microwave irradiation (200 Watt). Under these conditions, complete consumption of the starting diyne was observed after 1 hour and the product was isolated in 78% yield (entry 12). Therefore, it was concluded that microwave promotion offered no significant advantages over conventional heating of this reaction.

Interestingly, opposite to our analogous synthesis of 3,5-disubstituted-1,2-isoxazoles,[28] the high yields of **2a** observed were attained without the need of adding base to the reaction medium. This was rationalized as being the result of two main factors. First, the higher basicity of hydrazine (pK_b= 5.9) in comparison with hydroxylamine (pK_b= 8.0), which would favor the initial attack of the nitrogen to the 1,3-diyne system; secondly, the higher basicity of the intermediate resulting from reaction with hydrazine with regards to that generated by reaction with hydroxylamine, which would permit an easier final cyclization stage.

It was considered that the conditions of entry 10 were the best for the model system, representing an important improvement over previous methodologies, which employ the more environmentally problematic DMSO. The use of PEG-400 allowed the reaction to be successfully carried out in less time and employing lower amounts of both, solvent and hydrazine.[26a] Furthermore, these conditions were robust, taking into account the excellent yields recorded despite that no special precautions were taken to exclude oxygen or moisture from the reaction.

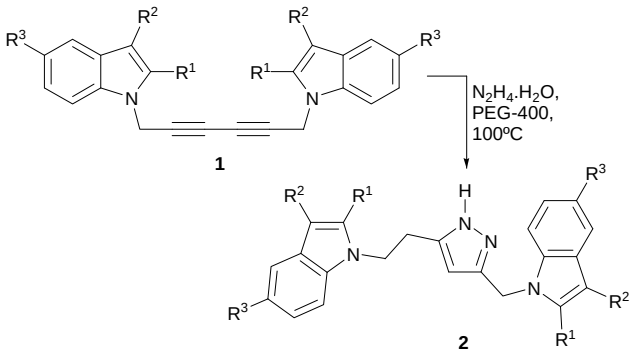
Having identified these optimal conditions, the stage was set to explore the scope of this one-pot and metal-free cyclization reaction. Initially, this was carried out employing a set of symmetrical diynes (**1a-f**). Gratifyingly, it was observed (Table 2) that the attained yields of 1*H*-3,5-disubstituted pyrazoles (**2a-f**) ranged from good to excellent (68-89%).

In addition, it was detected that the reaction seemed to be somewhat sensitive to steric strain, since longer reaction times were required when the starting indoles carried out a substituent on C-2 (entry 4) or when a carbazole was employed instead of an indole as the end-capping heterocyclic moiety (entry 6). The reaction was also slower in the case of the 5-methoxy and 5-(*p*-tolyl) substituted derivatives (entries 2 and 5).

After successfully achieving access to the proposed 3,5-disubstituted 1*H*-pyrazoles (**2**) from symmetric 1,3-diynes, it was decided to further investigate the reaction limits, by expanding its scope to the synthesis of pyrazoles resulting from non-symmetric 1,3-diynes. The results of this endeavor are detailed in Table 3.

The initial experiments were carried out with 1-(5-phenylpenta-2,4-diynyl)-1*H*-indole (**3a**, 0.3 mmol) and hydrazine hydrate (24% in H_2O, 2.0 equiv.) in PEG-400 (0.5 mL). These revealed that under the previously optimized conditions, the expected 3,5-disubstituted 1*H*-pyrazole **4a** was obtained in 89% yield, admixed with some unreacted starting material (entry 1).

Table 2. Synthesis of 3,5-disubstituted 1*H*-pyrazoles **2a-f** from symmetric 1,3-diyne indole derivatives **1a-f**.[a]



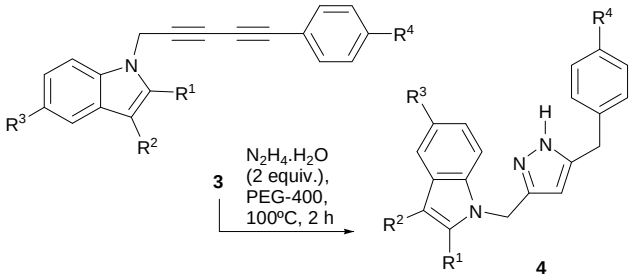
Entry Nº	St. Mat./ Prod. Nº	R^1	R^2	R^3	Time (h)	Yield (%)
1	**1a/2a**	H	H	H	1	89
2	**1b/2b**	H	H	OMe	3	77
3	**1c/2c**	H	H	Br	1	82
4	**1d/2d**	Me	H	H	3	68
5	**1e/2e**	H	H	4-Me-C_6H_4	2	73
6	**1f/2f**	CH=CH-CH=CH		H	5	89

[a] Reaction conditions: Diyne (**1**, 0.3 mmol); $N_2H_4.H_2O$ (2 equiv.); PEG-400 (0.5 mL).

However, it was observed that increasing the reaction time to 2 h afforded 96% of **4a**. Therefore, the next series of transformations were carried out by heating 2 h at 100ºC.

Interestingly, opposite to other reactions toward pyrazoles or 1,2-isoxazoles,[26a] which resulted in mixtures of isomers when non-symmetric starting materials are employed, in this case, the transformation was regio- and chemoselective, advantageously affording **4a**. The factors governing the chemoselectivity of the addition of nucleophiles to 1-phenyl 4-substituted 1,3-butadiynes carrying an heteroatom attached to the propargylic position have been discussed.[30]

Table 3. Synthesis of 3,5-disubstituted 1*H*-pyrazoles **4** from non-symmetric 1,3-diyne indole derivatives **3**.[a]



Entry Nº	St. Mat./ Prod. Nº	R^1	R^2	R^3	R^4	Yield (%)
1	**3a/4a**	H	H	H	H	89[b]
2	**3a/4a**	H	H	H	H	96
3	**3b/4b**	H	H	H	Me	92
4	**3c/4c**	H	H	OMe	H	93
5	**3d/4d**	H	H	Br	Me	83
6	**3e/4e**	CH=CH-CH=CH		H	H	86
7	**3f/4f**	CH=CH-CH=CH		H	Me	84

[a] Reaction conditions: Diyne (0.3 mmol); PEG-400 (0.5 mL).

[b] The reaction was carried out during 1 h at 100ºC.

Applying the optimized conditions to 1,4-disubstituted 1,3-diynes differently functionalized on both, the indole and the phenyl units, afforded the expected products (**4a-f**) in excellent yields (83-96%), as single isomers, as stemmed from analysis of their ^{1}H and ^{13}C NMR spectra. For example, the ^{1}H NMR spectrum of **4f** exhibited three singlets in the upfield region, corresponding to the protons of the methylene groups attached to the pyrazole ring [δ 3.77 (s, 2H) and 5.49 (s, 2H) ppm] and the methyl group of the *p*-tolyl unit [δ 2.21 (s, 3H) ppm]. On the other hand, its ^{13}C NMR spectrum displayed three signals at δ 20.5, 30.6 and 40.3 ppm (overlapped with the signal of the solvent), which proved to correlate with the methyl and methylene protons, respectively, in the HSQC spectrum.

In continuation of this work, it was decided to explore more in depth the scope of the reaction, by examining its performance in the synthesis of different 1-aryl-1*H*-pyrazoles, using arylhydrazines as the nucleophiles. This kind of transformation has been described only occasionally.[25a,35b] Furthermore, to date it has not been studied in detail, except for a recent report by the group of Bao, whi disclosed the synthesis of the related 1-alkyl-1*H*-pyrazoles by reaction of alkylhydrazines with 1,3-diynes under Et_2NH promotion, after prolonged heating in DMSO.[26b]

The proposed reaction was first optimized with 1,6-di-(1*H*-indol-1-yl)hexa-2,4-diyne (**1a**, 0.3 mmol) and phenylhydrazine (0.6 mmol) in PEG-400 (0.5 mL), employing the best conditions found for the synthesis of the 3,5-disubstituted 1*H*-pyrazoles **2** (Table 1, entry 10) as the starting point.

However, the formation of the desired product **5a** was observed in very low yield (15%, Table 4, entry 1), even after heating 24 hours at 100ºC. In addition, a careful examination of the ^{1}H NMR spectrum of the reaction mixture revealed the formation of minor amounts (< 7%) of an acompanying product, to which structure **5'a** was attributed on the basis of its spectal analysis.

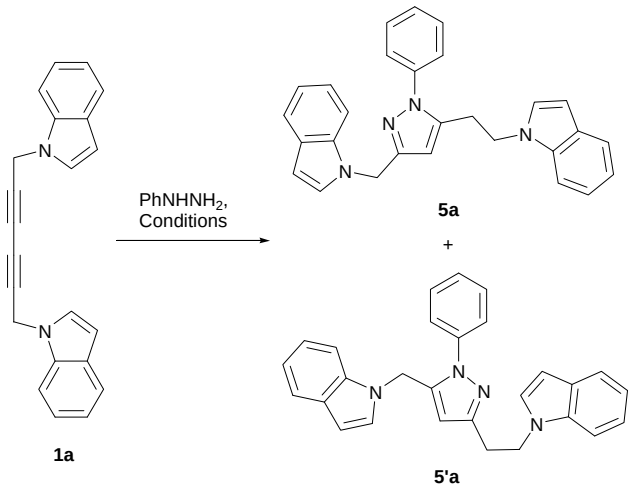
This was also confirmed by interpretation of its low resolution mass spectrum obtained by GC-MS analysis of the reaction mixture. Therefore, the selectivity of the nucleophilic attack of the arylhydrazine was also taken into account under each tested condition.

Interestingly, performing the pyrazolation reaction at 120ºC was of no help, affording a combined yield of only 14% of **5a/5'a** (entry 2), whilst retaining the reaction selectivity (14:1). Therefore, the influence of the relative proportion of phenylhydrazine on the outcome of the process was next screened, at 100ºC, increasing its amount to 5 equivalents (entries 3-5).

This modification duplicated the yields (entry 4) at the expense of a slight decrease in product selectivity (up to 11% **5'a**). In addition, the best yields attained (39%, entry 5) were considered far from optimal. However, a further increase in the quantity of phenylhydrazine to 10 equivalents resulted in a substantially better reaction performance, also reducing the reaction time when the transformation was carried out at 100ºC (entry 6).

Furthermore, raising the temperature to 110ºC enabled the transformation to be carried out in 5 h, with 76% yield without changes in its selectivity (entry 7). The use of basic additives (Et_3N, diisopropylethylamine, pyridine and 1,10-phenanthroline, 15 mol%) was also tested; however, it was found that their presence did not afford significant improvements in product yield; furthermore, addition of Et_3N, *i*-$PrNEt_2$ and pyridine resulted in diminished selectivity (7.5-8.6:1). Therefore, taking into account product yield and reaction selectivity, the conditions of entry 7 were considered the optimum.

Table 4. Optimization of the synthesis of 3,5-disubstituted 1-aryl-1*H*-pyrazoles **5/5'** from 1,3-diyne indole derivative **1a** and phenylhydrazine.[a]



Entry Nº	$PhNHNH_2$ (equiv.)	Temp. (°C)	Time (h)	Yield (%)	Ratio **5a:5'a**[b]
1	2.0	100	24	15	15:1
2	2.0	120	24	14	14:1
3	3.0	100	24	21	15:1
4	4.0	100	24	37	9:1
5	5.0	100	24	39	10:1
6	10.0	100	6	70	10:1
7	10.0	110	5	76	10:1
8[c]	10.0	110	5	44	>15:1
9[c]	10.0	110	20	-	-

[a] Reaction conditions: Diyne (**1a**, 0.3 mmol); PEG-400 (0.5 mL).

[b] Determined by ^{1}H NMR spectroscopy.

[c] DMSO (0.5 mL) was employed as reaction solvent.

For the sake of comparison with alternative protocols,[26b] the same reaction was carried out in DMSO, observing that only 44% of **5a** was formed after 5 h, accompanied by substantial amounts of unidentified degradation products (entry 8). However, leaving the system to react for 20 h resulted in complete destruction of the starting material and the formed products (entry 9), confirming the unsuitability of these conditions for the preparation of **5a**.

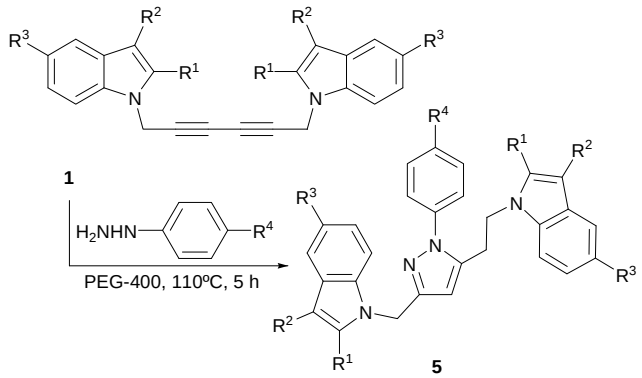
The structure of compound **5a** was confirmed by analysis of its NMR spectral data, especially its HMBC spectrum, where crosspeaks were found between the methylene protons [δ 3.01 (t, 2H) and δ 5.33 (s, 2H)] attached to C-3 and C-5 of the imidazole ring, and the ^{13}C resonances of these imidazole ring carbons (δ 141.3 and δ 149.7, respectively). In addition, both methylene protons exhibited correlations with C-4 (δ 104.7).

Other symmetric indole-derived diynes were treated with differently substituted phenylhydrazines and converted into their corresponding pyrazoles, as depicted in Table 5. Comparing the results of entries 1-4 revealed that the lowest yields were obtained when arylhydrazines having electron-withdrawing groups were employed (entries 2 and 3).

On the other hand, it was observed that the product yields

obtained with the substituted indoles (entries 5 and 6) and carbazole (entry 7) were lower than that achieved by their unsubstituted congener (entry 1).

Table 5. Synthesis of 3,5-disubstituted 1-aryl-1*H*-pyrazoles **5** from symmetric 1,3-diyne indole derivatives **1** and substituted phenylhydrazines.[a]

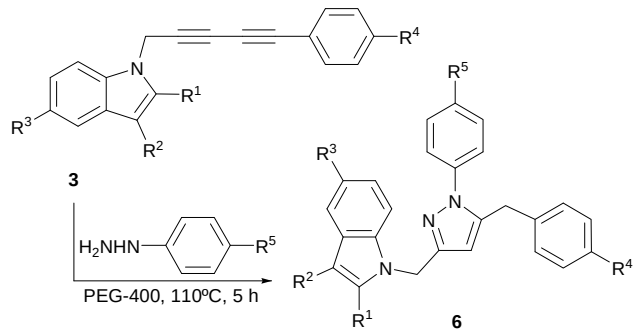


Run Nº	St. Mat./ Prod. Nº	R^1	R^2	R^3	R^4	Yield (%)	Ratio **5/5'**
1	**1a/5a**	H	H	H	H	75	10:1
2	**1a/5b**	H	H	H	Br	61	16:1
3	**1a/5c**	H	H	H	Cl	53	13:1
4	**1a/5d**	H	H	H	Me	62	6:1
5	**1b/5e**	H	H	OMe	H	65	14:1
6	**1c/5f**	H	H	Br	H	69	12:1
7	**1f/5g**	CH=CH-CH=CH		H	H	72	8:1

[a] Reaction conditions: Diyne (**1**, 0.3 mmol); arylhydrazine (10 equiv.); PEG-400 (0.5 mL).

Encouraged by the success of these reactions, the transformation was attempted with the non-symmetric 1,4-disubstituted 1,3-diynes (**3**), and the outcome is collected in Table 6.

Table 6. Synthesis of 3,5-disubstituted 1-aryl-1*H*-pyrazoles **6** from non-symmetric 1,3-diyne indole derivatives **3** and substituted phenylhydrazines.[a]



Run Nº	Comp. Nº	R^1	R^2	R^3	R^4	R^5	Yield (%)	Ratio **6/6'**
1	**3a/6a**	H	H	H	H	H	73	10:1
2	**3a/6b**	H	H	H	H	Br	55	16:1
3	**3a/6c**	H	H	H	H	Cl	50	10:1
4	**3a/6d**	H	H	H	H	Me	70	6:1
5	**3c/6f**	H	H	OMe	H	H	61	12:1
6	**3d/6e**	H	H	Br	Me	H	65	10:1
7	**3e/6g**	CH=CH-CH=CH		H	H	H	71	7:1

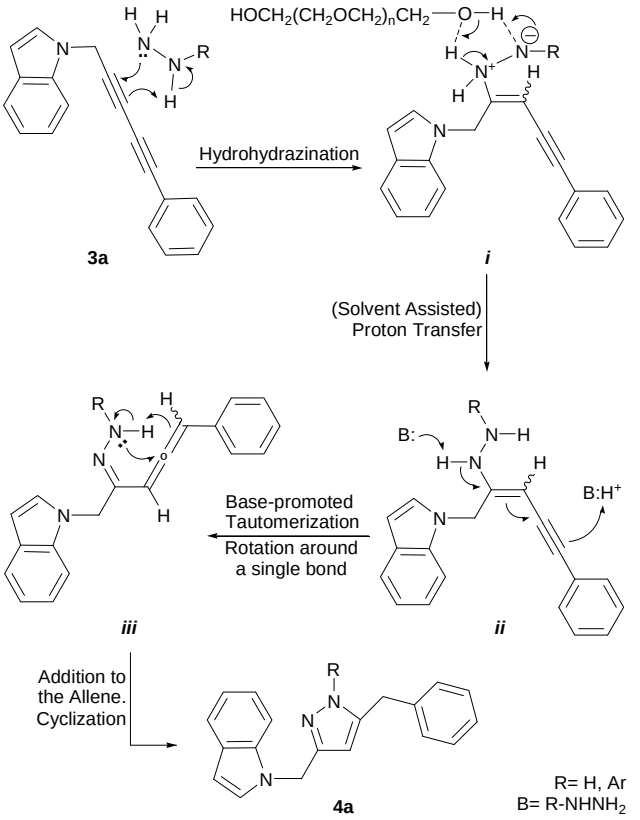
[a] Reaction conditions: Diyne (**3**, 0.3 mmol); arylhydrazine (10 equiv.); PEG-400 (0.5 mL).

The experiments revealed results quire similar in nature to those recorded for the symmetric diynes (Table 5). It was observed that the yields of the heterocycles formed by cyclization with arylhydrazines carrying electron withdrawing substituents (entries 2 and 3) were slightly lower than those verified for phenyl- and *p*-tolyl- hydrazine (entries 1 and 4, respectively). On the other hand, the use of substituted indoles (entries 5 and 6) or carbazole (entry 7) derivatives furnished lower yields and no better selectivity than their unsubstituted counterpart (entry 1).

Unfortunately, the pyrazoles were produced in mixtures with minor amounts of isomers, that could not be separated even after three successive chromatographies nor by crystallization, and no suitable crystals for X-ray analysis of the so formed pyrazoles could be obtained; however, the interpretation of the NMR data of the compounds allowed the unequivocal structural assignment of the heterocycles.

As a working hypothesis, we propose that this transformation takes place through the plausible mechanism shown in Scheme 2, reminiscent to that projected to be involved in the synthesis of the related 3,5-disubstituted 1,2-isoxazoles from 1,3-diynes.[28,31] and a less detailed sequence put forward by Bao *et al.*[26a]

In this scenario, the cyclization is triggered by the hydrohydrazination[32] of the 1,4-disubstituted 1,3-diyne (**3a**), which is a variation of the Cope-type hydroamination reaction.[33] Under the optimized conditions, the transformation is highly regioselective, taking place by attack of the least hindered nitrogen atom of the hydrazine to one of the outer carbon atoms of the 1,3-diyne in a Markovnikov fashion, to give a *N*-ene-yne hydrazine (***i***) intermediate.



Scheme 2. Proposed reaction mechanism for the synthesis of the 3,5-disubstituted 1*H*- and 1-aryl-1*H*- pyrazoles carrying indole derivatives.

Noteworthy, opposite to most of the hydrohydrazination processes recorded in the literature, which are promoted or catalyzed by organometallic complexes of Ti, Rh, Ir, Co, Au or Zn,[34] and afford mainly Markovnikov products,[35] this step entails an advantageous metal-free transformation which takes place under relatively mild conditions. Furthermore, the observed selectivity is relevant, since alkylhydrazines have also been observed to afford the anti-Markovnikov adducts upon metal-free reaction with phenylacetylenes.[33b]

In turn, the *N*-ene-yne hydrazine ***i*** can undergo a proton transfer toward intermediate ***ii***. Presumably, this step would require some solvent assistance, underscoring the importance of PEG-400 as a convenient reaction medium, more suitable than other previously used solvents.[26a,b]

Interestingly, despite the stereochemistry of the double bond in ***i*** was not assessed, the metal-free (uncatalyzed) hydroamination of conjugated diynes, as well as its analogous hydroalkoxylation, hydrothiolation, hydroselenation, hydrotelluration and hydrophosphination reactions, has been shown to afford mixtures ene-yne products, always favoring the *Z*-isomer, as a result of an *anti*-addition of the attacking species, under solvent assistance,[36] also emphasizing the importance of solvent selection.

Despite that the hydrohydrazination of 1,3-diynes may furnish an analogous outcome, in the current case the following reaction steps ensure that cyclization to the pyrazole can be achieved regardless of the geometry of the starting hydrohydrazination product.

Next, the *N*-ene-yne hydrazine ***ii*** can undergo a base promoted tautomerization[37] to the corresponding α-allenyl hydrazone ***iii***. The basicity of the hydrazine (pK_b= 5.9) is substantially lower than that of similar amines, and it decreases with increasing substitution; thus, methylhydrazine has a slightly higher pK_b= 6.1, whereas phenylhydrazine has a pK_b= 9.8.[38] Therefore, although the basicity of hydrazine itself may have sufficed to promote the ene-yne hydrazine to α-allenyl hydrazone rearrangement (***ii*** → ***iii***), it seems likely that in the case of arylhydrazines, these differences account for the need of a higher excess of reagent and slightly harsher conditions to be successful.[37c]

Oposite to other mechanistic proposals, where direct intramolecular hydroamination of an alkyne, followed by double bond isomerization, results in the expected 3,5-disubstituted pyrazole,[14a] the outcome of the current transformation suggests that α-allenyl hydrazones must be reaction intermediates. Interestingly, the ultrasound-mediated preparation of 3,5-disubstituted pyrazoles from allenyl ketones has been proposed to take place through initial conjugate attack to the allenyl moiety, closing the heterocyclic ring by attack to the carbonyl moiety followed by dehydration,[14b] and the synthesis of fused pyrazoles from certain β-allenyl hydrazones has been reported.[39]

At this point, rotation of the allenyl moiety around the Csp^2-Csp^2 single bond would then establish the proper geometry of the α-allenyl hydrazone intermediate for the subsequent intramolecular thermal hydroamination of the distal double bond of the allene moiety[13c,40] toward the final product (**4a**). By analogy with the cyclization of β-allenyl hydrazones to *N*-aminosubstituted pyrroles,[41] no six-membered ring products were observed, probably because the central carbon atom of the intermediate allenic system is more succeptible to nucleophilic attack than the outer pair of carbon nuclei.[42] The outer carbon becomes more stable once the π-bond with the central carbon atom breaks, since it becames able to make four sigma bonds, which is carbon's most stable configuration. This process entails a 5-*exo*-*dig* type cyclization,[35b] which has seen some recent precedents in the synthesis of pyrazoles involving alkyne intermediates.[14a]

Conclusions

In summary, we have developed a one-pot convenient, robust and efficient procedure for the regioselective synthesis of 3,5-disubstituted 1*H*-pyrazoles from 1,4-disubstituted 1,3-diynes carrying indole moieties in PEG-400 as an eco-friendly solvent. Unlike similar transformations, the process did not require metal catalysis nor added acids or bases, despite the lower basicity of arylhydrazines relative to hydrazine.

The synthesis involved two sequential hydroamination reactions, being triggered by a regioselective Markovnikov-type hydrohydrazination of the starting 1,3-diyne, followed by rearrangement of the resulting ene-yne intermediate to an α-allenyl hydrazone, and a second hydroamination to produce the final 5-*exo*-*dig* cyclization toward the heterocycle.

The scope and limitations of the protocol were tested with a wide range of symmetric and non-symmetric 1,3-diynes, as well as with hydrazine and arylhydrazines. The transformation demonstrated to exhibit excellent tolerance to a variety of substituents on both reactants. Sterically hindered substrates also underwent the reaction, albeit at a slower pace. However, the use of PEG-400 as reaction medium enabled the transformation to be carried out in relatively short reaction times,[26a] and under mild conditions.

In addition, since the transformation is not sensitive to air (oxygen) and moisture, it is an ideal and cost-effective alternative for the bulk synthesis of substituted pyrazoles, at the same time that its operational simplicity makes it attractive for building libraries of pyrazoles in the fields of combinatorial chemistry and drug discovery.

Experimental section

General information

PEG-400 and other commercial reagents were used without further purification. In the conventional purification procedure, the crude material was submitted to flash column chromatography with silica gel 60 H (particle size 40-63 μm, 230-400 mesh), eluting isocratically with mixtures of hexane:EtOAc.

All new compounds gave single spots when run on TLC plates of Kieselgel 60 GF_{254}, employing different hexane-EtOAc solvent systems. Chromatographic spots were detected by irradiation of the plates with UV light (254 nm), followed by exposure to iodine vapors of by spraying with ethanolic vanillin/sulfuric acid reagent and careful heating.

Apparatus

The melting points were measured on an MQAPF-301

(Microquímica) instrument and are reported uncorrected. The infrared spectra were acquired on a Shimadzu Prestige-21 spectrometer, with the samples prepared as KBr pellets or thin films held between NaCl disks. The NMR spectra (^{1}H and ^{13}C) were recorded in $CDCl_3$ unless otherwise noted, on Bruker DPX-400 and Bruker DPX-600 spectrometers (400 and 600 MHz for ^{1}H, respectively). Chemical shift data are reported in ppm downfield from TMS, employed as internal standard. Coupling constants (*J*) are informed in Hertz. Elemental analyses were recorded on a Perkin-Elmer CHN 2400 analyzer. The low resolution mass spectra were acquired on a Shimadzu QP2010 *Plus* CG-MS instrument. High-resolution mass spectral data were obtained in a Bruker microTOF-Q II instrument. Detection of the ions was performed with electrospray ionization in positive ion mode.

General procedure for the preparation of the 1*H*-3,5-disubstituted pyrazoles 2a-f and 4a-f

A stirred solution of the diyne (**1** or **3**, 0.3 mmol)[28] in PEG-400 (0.5 mL), contained in a test tube, was treated with an aqueous solution of $H_2NNH_2.H_2O$ (24%, 0.125 mL, 0.6 mmol, 2 equiv.). The reaction was heated at 100ºC until complete consumption of starting material was ascertained by TLC. Then, the system was allowed to cool to room temperature, H_2O (10 mL) was added, and the product was extracted with EtOAc (3 x 25 ml). The combined organic layers were dried over $MgSO_4$, the solvent was evaporated under reduced pressure and the residue was purified by column chromatography eluting with a hexane:EtOAc mixtures. A 50:50 mixture was employed for pyrazoles **2a-f** and a 60:40 mixture for pyrazoles **4a-f**.

1-((5-(2-(1*H*-Indol-1-yl)ethyl)-1*H*-pyrazol-3-yl)methyl)-1*H*-indole (2a)

Beige solid, m.p.: 96-98 °C; yield: 89%. ^{1}H NMR (400 MHz) δ: 2.84 (t, *J* = 6.9, 2H), 4.11 (t, *J* = 6.9, 2H), 5.08 (s, 2H), 5.66 (s, 1H), 6.36 (d, *J* = 3.1, 1H), 6.46 (d, *J* = 3.1, 1H), 6.73 (d, *J* = 3.1, 1H), 6.98 (d, *J* = 3.1, 1H), 7.03-7.16 (m, 5H), 7.25 (d, *J* = 8.1, 1H), 7.55-7.60 (m, 2H) and 7.71 (bs, 1H). ^{13}C NMR (100 MHz) δ: 27.1, 43.2, 45.7, 101.4, 101.7, 103.2, 109.1, 109.5, 119.5, 119.6, 120.9, 121.0, 121.6, 121.7, 127.7, 127.8, 128.6, 128.7, 135.5, 136.1, 143.7 and 147.0. IR (KBr, ν): 3448, 3100, 3051, 2929, 1707, 1612, 1512, 1481, 1462, 1428, 1313, 1213, 1011 and 741 cm^{-1}. EI-MS (*m/z*, rel. int., %): 341 (6, $[M+1]^+$), 340 (24, M^+), 131 (11), 130 (100), 103 (9) and 77 (12). HRMS (ESI–TOF, *m/z*): Found 363.1586; $C_{22}H_{20}N_4Na$ $(M+Na)^+$ requires 363.1586.

5-Methoxy-1-((5-(2-(5-methoxy-1*H*-indol-1-yl)ethyl)-1*H*-pyrazol-3-yl) methyl)-1*H*-indole (2b)

Beige solid, m.p.: 104-106 °C; yield: 77%. ^{1}H NMR (400 MHz) δ: 2.88 (t, *J* = 6.9, 2H), 3.78 (s, 3H), 3.79 (s, 3H), 4.11 (t, *J* = 6.9, 2H), 5.06 (s, 2H), 5.67 (s, 1H), 6.29 (d, *J* = 2.9, 1H), 6.38 (d, *J* = 2.9, 1H), 6.74 (d, *J* = 3.1, 1H), 6.78 (dd, *J* = 8.9 and 2.4, 1H), 6.81 (dd, *J* = 8.9 and 2.4, 1H), 6.97 (d, *J* = 3.1, 1H), 7.01 (d, *J* = 8.9, 1H), 7.02 (d, *J* = 2.4, 1H), 7.05 (d, *J* = 2.3, 1H), 7.12 (d, *J* = 8.9, 1H) and 7.52 (bs, 1H). ^{13}C NMR (100 MHz) δ: 27.2, 43.3, 45.9, 55.8, 101.0, 101.3, 102.7, 102.8, 103.2, 109.8, 110.2, 111.9, 112.0, 128.2, 128.4, 129.0, 129.1, 130.9, 131.4, 143.8, 147.0, 154.0 and 154.1. IR (film, ν): 3360, 3261, 2933, 1702, 1621, 1576, 1488, 1450, 1239, 1151, 1029, 799 and 720 cm^{-1}. EI-MS (*m/z*, rel. int., %): 401 (11, $[M+1]^+$), 400 (38, M^+), 161 (14), 160 (100), 145 (10), 117 (26) and 83 (15). Anal. Calc.: C, 71.98; H, 6.04; N, 13.99. Found: C, 71.46; H, 5.92; N, 14.01.

5-Bromo-1-((5-(2-(5-bromo-1*H*-indol-1-yl)ethyl)-1*H*-pyrazol-3-yl) methyl)-1*H*-indole (2c)

Beige waxy solid; yield: 82%. ^{1}H NMR (400 MHz) δ: 2.90 (t, *J* = 6.7, 2H), 4.15 (t, *J* = 6.7, 2H), 5.06 (s, 2H), 5.62 (s, 1H), 6.28 (dd, *J* = 3.2 and 0.6, 1H), 6.39 (dd, *J* = 3.2 and 0.6, 1H), 6.75 (d, *J* = 3.2, 1H), 6.94 (d, *J* = 8.7, 1H), 6.97 (d, *J* = 3.2, 1H), 7.07 (d, *J* = 8.7, 1H), 7.13 (dd, *J* = 8.7 and 1.9, 1H), 7.21 (dd, *J* = 8.7 and 1.9, 1H), 7.66 (d, *J* = 1.9, 1H) and 7.70 (d, *J* = 1.9, 1H). ^{13}C NMR (100 MHz) δ: 27.2, 43.3, 45.9, 101.2, 101.5, 103.4, 110.5, 110.9, 112.8, 113.0, 123.4, 123.5, 124.4, 124.5, 128.7, 129.0, 130.2, 130.4, 134.3, 134.7, 143.5 and 146.7. IR (KBr, ν): 3396, 3131, 2927, 1703, 1508, 1468, 1329, 1276, 1050, 794, 754 and 719 cm^{-1}. EI-MS (*m/z*, rel. int., %): 498 (14, M^+), 419 (28), 417 (27), 210 (63), 208 (70), 129 (41), 84 (13) and 43 (100). Anal. Calc.: C, 53.04; H, 3.64; N, 11.25. Found: C, 53.08; H, 3.70; N, 11.05.

2-Methyl-1-((5-(2-(2-methyl-1*H*-indol-1-yl)ethyl)-1*H*-pyrazol-3-yl) methyl)-1*H*-indole (2d)

Brown solid, m.p.: 110-112 °C; yield: 68%. ^{1}H NMR (400 MHz) δ: 1.99 (s, 3H), 2.35 (s, 3H), 2.85 (t, *J* = 6.9, 2H), 4.11 (t, *J* = 6.9, 2H), 5.14 (s, 2H), 5.53 (s, 1H), 6.11 (s, 1H), 6.25 (s, 1H), 7.01-7.11 (m, 5H), 7.23 (d, *J* = 8.0, 1H) and 7.46-7.51 (m, 3H). ^{13}C NMR (100 MHz) δ: 12.2, 12.6, 26.7, 40.2, 42.6, 100.2, 100.5, 102.8, 108.7, 109.0, 119.5, 119.5, 119.7, 119.8, 120.6, 120.7, 128.2, 128.2, 136.1, 136.4, 136.4, 136.9, 143.5 and 147.7. IR (KBr, ν): 3378, 3049, 2934, 1703, 1614, 1462, 1399, 1342, 1164, 1117, 773 and 746 cm^{-1}. EI-MS (*m/z*, rel. int., %): 368 (33, M^+), 281 (43), 207 (100), 144 (98), 130 (23) and 73 (38). HRMS (ESI–TOF, *m/z*): Found 391.1891; $C_{24}H_{20}N_4Na$ $(M+Na)^+$ requires 391.1899.

5-*p*-Tolyl-1-((5-(2-(5-*p*-tolyl-1*H*-indol-1-yl)ethyl)-1*H*-pyrazol-3-yl) methyl)-1*H*-indole (2e)

Brown solid, m.p.: 80-82 °C; yield: 73%. ^{1}H NMR (400 MHz) δ: 2.37 (s, 6H), 2.85 (t, *J* = 6.7, 2H), 4.11 (t, *J* = 6.7, 2H), 5.10 (s, 2H), 5.70 (s, 1H), 6.39 (d, *J* = 3.1, 1H), 6.49 (d, *J* = 3.1, 1H), 6.73 (d, *J* = 3.1, 1H), 7.00 (d, *J* = 3.1, 1H), 7.12 (d, *J* = 8.5, 2H), 7.18-7.21 (m, 5H), 7.27 (d, *J* = 8.5, 2H), 7.33 (dd, *J* = 8.5 and 1.6, 1H), 7.37 (dd, *J* = 8.5 and 1.6, 1H), 7.48-7.50 (m, 5H) and 7.78 (dd, *J* = 8.5 and 1.6, 2H). ^{13}C NMR (100 MHz) δ: 21.0, 27.1, 43.4, 45.9, 101.7, 102.0, 103.2, 109.3, 109.7, 119.1, 119.2, 121.3, 121.4, 127.0, 127.1, 128.3, 128.5, 129.0, 129.1, 129.3, 129.4, 132.9, 133.0, 134.9, 135.4, 135.9, 135.9, 139.3, 139.4, 143.5 and 147.1. IR (film, ν): 3375, 3021, 2919, 1696, 1615, 1571, 1478, 1448, 1334, 1259, 1180, 825, 798, 762 and 721 cm^{-1}. EI-MS (*m/z*, rel. int., %): 521 (13, $[M+1]^+$), 520 (31, M^+), 221 (18), 220 (100) and 204 (9). HRMS (ESI–TOF, *m/z*): Found 543.2507; $C_{36}H_{32}N_4Na$ $(M+Na)^+$ requires 543.2525.

9-((5-(2-(9*H*-Carbazol-9-yl)ethyl)-1*H*-pyrazol-3-yl)-methyl)-

9*H*-carbazole (2f)

White solid, m.p.: 178-180 °C; yield: 89%. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 2.94 (t, *J* = 7.5, 2H), 4.49 (t, *J* = 7.5, 2H), 5.47 (s, 2H), 5.94 (s, 1H), 7.14 (t, *J* = 7.4, 2H), 7.20 (t, *J* = 7.4, 2H), 7.30-7.33 (m, 2H), 7.43-7.48 (m, 4H), 7.65 (d, *J* = 8.2, 2H), 8.08 (d, *J* = 7.7, 2H) and 8.13 (d, *J* = 7.7, 2H). ^{13}C NMR (100 MHz, DMSO-d_6) δ: 24.9, 40.3, 42.0, 102.4, 108.9, 109.3, 118.5, 118.6, 119.9, 119.9, 121.9, 122.0, 125.3, 125.4, 139.5 and 139.8. IR (KBr, ν): 3167, 3052, 2923, 1625, 1597, 1486, 1459, 1455, 1452, 1329, 1235, 1153, 1003, 746, 744 and 720 cm^{-1}. EI-MS (*m/z*, rel. int., %): 441 (13, $[M+1]^+$), 440 (45, M^+), 181 (19), 180 (100), 167 (37) and 152 (17). HRMS (ESI–TOF, *m/z*): Found 463.1872; $C_{30}H_{24}N_4Na$ $(M+Na)^+$ requires 463.1899.

1-((5-Benzyl-1*H*-pyrazol-3-yl)methyl)-1*H*-indole (4a)

Red solid, m.p.: 48-50 °C; yield: 96%. ^{1}H NMR (400 MHz) δ: 3.76 (s, 2H), 5.13 (s, 2H), 5.78 (s, 1H), 6.46 (d, *J* = 3.0, 1H), 7.04-7.09 (m, 4H), 7.12-7.21 (m, 4H), 7.31 (d, *J* = 8.2, 1H), 7.59 (d, *J* = 7.8, 1H) and 8.41 (bs, 1H). ^{13}C NMR (100 MHz) δ: 32.4, 43.5, 101.6, 103.3, 109.5, 119.5, 120.9, 121.6, 126.7, 127.8, 128.5, 128.6, 128.7, 136.2, 137.8, 145.2 and 147.8. IR (KBr, ν): 3194, 3025, 2921, 1694, 1573, 1488, 1463, 1314, 1180, 1005, 799, 742 and 710 cm^{-1}. EI-MS (*m/z*, rel. int., %): 288 (11, $[M+1]^+$), 287 (50, M^+), 171 (30), 117 (100) and 91 (11). HRMS (ESI–TOF, *m/z*): Found 310.1319; $C_{19}H_{17}N_3Na$ $(M+Na)^+$ requires 310.1320.

1-((5-(4-Methylbenzyl)-1*H*-pyrazol-3-yl)methyl)-1*H*-indole (4b)

Beige solid, m.p.: 97-99 °C; yield: 92%. ^{1}H NMR (400 MHz) δ: 2.28 (s, 3H), 3.81 (s, 2H), 5.20 (s, 2H), 5.81 (s, 1H), 6.49 (dd, *J* = 3.1 and 0.7, 1H), 7.00 (d, *J* = 8.0, 2H), 7.07 (d, *J* = 7.7, 2H), 7.09-7.11 (m, 2H), 7.15-7.19 (m, 1H), 7.34 (d, *J* = 8.0, 1H), 7.61 (d, *J* = 7.7, 1H) and 7.68 (bs, 1H). ^{13}C NMR (100 MHz) δ: 20.9, 31.9, 43.3, 101.8, 103.4, 109.5, 119.5, 120.9, 121.7, 127.9, 128.5, 128.7, 129.4, 134.3, 136.1, 136.4, 145.7 and 147.8. IR (KBr, ν): 3194, 2921, 1704, 1613, 1572, 1513, 1463, 1313, 1005 and 743 cm^{-1}. EI-MS (*m/z*, rel. int., %): 302 (13, $[M+1]^+$), 301 (51, M^+), 185 (28) and 117 (100). Anal. Calc.: C, 79.70; H, 6.35; N, 13.94. Found: C, 79.17; H, 6.07; N, 13.75.

1-((5-Benzyl-1*H*-pyrazol-3-yl)methyl)-5-methoxy-1*H*-indole (4c)

Brown oil; yield: 93%. ^{1}H NMR (400 MHz) δ: 3.79 (s, 3H), 3.80 (s, 2H), 5.12 (s, 2H), 5.80 (s, 1H), 6.38 (dd, *J* = 3.1 and 0.8, 1H), 6.81 (dd, *J* = 8.8 and 2.4, 1H), 7.04 (d, *J* = 3.1, 1H), 7.05 (d, *J* = 2.4, 1H), 7.07-7.09 (m, 2H), 7.15-7.25 (m, 4H) and 8.25 (bs, 1H). ^{13}C NMR (100 MHz) δ: 32.4, 43.6, 55.8, 101.2, 102.9, 103.4, 110.2, 111.9, 126.7, 128.4, 128.5, 128.6, 129.1, 131.6, 137.7, 145.4, 147.7 and 154.2. IR (film, ν): 3193, 3100, 2937, 2832, 1620, 1574, 1486, 1446, 1341, 1237, 1149, 1029, 800, 748 and 719 cm^{-1}. EI-MS (*m/z*, rel. int., %): 318 (25, $[M+1]^+$), 317 (98, M^+), 171 (41), 148 (11), 147 (100), 132 (36), 119 (13) and 91 (14). HRMS (ESI–TOF, *m/z*): Found 340.1417; $C_{20}H_{19}N_3NaO$ $(M+Na)^+$ requires 340.1426.

5-Bromo-1-((5-(4-methylbenzyl)-1*H*-pyrazol-3-yl)methyl)-1*H*-indole (4d)

Beige solid, m.p.: 109-111 °C; yield: 83%. ^{1}H NMR (400 MHz) δ: 2.28 (s, 3H), 3.80 (s, 2H), 5.14 (s, 2H), 5.79 (s, 1H), 6.40 (d, *J* = 3.1, 1H), 6.99 (d, *J* = 8.0, 2H), 7.06 (d, *J* = 8.0, 2H), 7.09 (d, *J* = 3.1, 1H), 7.16-7.22 (m, 2H), 7.70 (d, *J* = 1.5, 1H) and 8.65 (bs, 1H). ^{13}C NMR (100 MHz) δ: 21.0, 31.8, 43.7, 101.2, 103.2, 111.1, 112.8, 123.3, 124.4, 128.4, 129.1, 129.4, 130.3, 134.2, 134.7, 136.5, 145.2 and 147.8. IR (KBr, ν): 3450, 3173, 3016, 2925, 2870, 1569, 1511, 1469, 1434, 1334, 1275, 1184, 1007, 820, 789, 761 and 712 cm^{-1}. EI-MS (*m/z*, rel. int., %): 381 (67, $[M+2]^+$), 379 (70, M^+), 197 (55), 195 (57), 186 (14), 185 (100), 115 (17) and 91 (12). HRMS (ESI–TOF, *m/z*): Found 402.0570; $C_{20}H_{18}BrN_3Na$ $(M+Na)^+$ requires 402.0582.

9-((5-Benzyl-1*H*-pyrazol-3-yl)methyl)-9*H*-carbazole (4e)

White solid, m.p.: 143-145 °C; yield: 86%. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 3.81 (s, 2H), 5.48 (s, 2H), 5.77 (s, 1H), 7.14-7.22 (m, 7H), 7.42 (t, *J* = 7.3, 2H), 7.66 (d, *J* = 8.0, 2H), 8.11 (d, *J* = 7.5, 2H) and 12.50 (bs, 1H). ^{13}C NMR (100 MHz, DMSO-d_6) δ: 31.8, 40.3, 102.1, 109.3, 118.6, 119.9, 122.0, 125.4, 125.9, 128.1, 128.1 and 139.8. IR (KBr, ν): 3398, 3178, 3092, 3022, 2930, 2865, 1599, 1487, 1457, 1330, 1001, 751 and 721 cm^{-1}. EI-MS (*m/z*, rel. int., %): 338 (13, $[M+1]^+$), 337 (50, M^+), 171 (23) and 167 (100). HRMS (ESI–TOF, *m/z*): Found 360.1471; $C_{23}H_{19}N_3Na$ $(M+Na)^+$ requires 360.1477.

9-((5-(4-Methylbenzyl)-1*H*-pyrazol-3-yl)methyl)-9*H*-carbazole (4f)

White solid, m.p.: 167-169 °C; yield: 84%. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 2.21 (s, 3H), 3.77 (s, 2H), 5.49 (s, 2H), 5.75 (s, 1H), 7.03 (s, 4H), 7.20 (t, *J* = 7.3, 2H), 7.44 (t, *J* = 7.6, 2H), 7.69 (d, *J* = 8.2, 2H), 8.13 (d, *J* = 7.7, 2H) and 12.53 (bs, 1H). ^{13}C NMR (100 MHz, DMSO-d_6) δ: 20.5, 30.6, 40.3, 102.0, 109.4, 118.7, 120.0, 122.0, 125.5, 128.1, 128.8, 135.0 and 135.8. IR (KBr, ν): 3418, 3175, 3015, 2928, 2863, 1599, 1485, 1458, 1328, 1200, 1151, 1004, 800, 746 and 718 cm^{-1}. EI-MS (*m/z*, rel. int., %): 352 (22, $[M+1]^+$), 351 (71, M^+), 185 (29), 180 (14), 168 (21), 167 (100), 129 (14), 91 (11) and 84 (88). Anal. Calc.: C, 82.02; H, 6.02; N, 11.96. Found: C, 81.48; H, 5.96; N, 11.64.

General procedure for the preparation of the 1*H*-3,5-disubstituted 1-aryl-1*H*-pyrazoles 5a-g and 6a-g

A stirred solution of the diyne (**1** or **3**, 0.3 mmol)[28] in PEG-400 (0.5 mL), contained in a test tube, was treated with the corresponding arylhydrazine (3 mmol, 10 equiv.).[43] The reaction was heated at 110ºC until complete consumption of starting material was ascertained by TLC. Then, the system was allowed to cool to room temperature, H_2O (10 mL) was added, and the product was extracted with EtOAc (3 x 25 ml). The combined organic layers were dried over $MgSO_4$, the solvent was evaporated under reduced pressure and the residue was purified by column chromatography eluting with a hexane:EtOAc mixtures. A 90:10 mixture was employed for pyrazoles **5a-g** and **6a-g**.

1-((5-(2-(1*H*-Indol-1-yl)ethyl)-1-phenyl-1*H*-pyrazol-3-yl) methyl)-1*H*-indole (5a)

Orange waxy solid; yield: 75%. ^{1}H NMR (600 MHz) δ: 3.01 (t, *J* = 7.4, 2H), 4.12 (t, *J* = 7.4, 2H), 5.33 (s, 2H), 5.90 (s, 1H), 6.36 (d, *J* = 3.1, 1H), 6.56 (d, *J* = 3.1, 1H), 6.73 (d, *J* = 3.1, 1H), 6.90-6.92 (m, 1H), 7.04-7.07 (m, 2H), 7.11-7.15 (m, 3H), 7.20 (d, *J* = 3.1, 1H), 7.21-7.25 (m, 1H), 7.33-7.37 (m, 3H), 7.46 (d, *J* = 8.2, 1H), 7.55-7.57 (m, 1H) and 7.66 (d, *J* = 7.9, 1H). ^{13}C NMR (150 MHz) δ: 27.1, 44.2, 45.5, 101.6, 101.7, 104.7, 108.8, 109.7, 119.4, 119.5, 120.9, 121.0, 121.6, 121.6, 125.6, 127.4, 128.0, 128.4, 128.6, 128.7, 129.3, 135.4, 136.2, 138.9, 141.3 and 149.7. IR (KBr, ν): 2925, 2852, 1597, 1502, 1462, 1314, 1180, 1015, 763, 741 and 696 cm^{-1}. EI-MS (*m/z*, rel. int., %): 417 (7, $[M+1]^+$), 416 (24, M^+), 169 (8), 130 (100), 103 (9) and 77 (13). Anal. Calc.: C, 80.74; H, 5.81; N, 13.45. Found: C, 80.00; H, 5.72; N, 13.18.

1-((5-(2-(1*H*-Indol-1-yl)ethyl)-1-(4-bromophenyl)-1*H*-pyrazol-3-yl) methyl)-1*H*-indole (5b)

Orange waxy solid; yield: 61%. ^{1}H NMR (400 MHz) δ: 2.97 (t, *J* = 7.0, 2H), 4.11 (t, *J* = 7.0, 2H), 5.29 (s, 2H), 5.90 (s, 1H), 6.33 (dd, *J* = 3.1 and *J* = 0.6, 1H), 6.55 (dd. *J* = 3.1 and *J* = 0.6, 1H), 6.65 (d, *J* = 3.1, 1H), 6.82-6.85 (m, 2H), 6.87-6.89 (m, 1H), 7.05-7.07 (m, 2H), 7.10-7.14 (m, 1H), 7.17 (d, *J* = 3.1, 1H), 7.20-7.24 (m, 1H), 7.34-7.38 (m, 2H), 7.43 (d, *J* = 8.2, 1H), 7.54-7.56 (m, 1H) and 7.65 (d, *J* = 7.9, 1H). ^{13}C NMR (100 MHz) δ: 26.9, 44.2, 45.7, 101.7, 101.8, 104.9, 108.7, 109.7, 119.6, 119.6, 121.0, 121.1, 121.7, 121.7, 122.1, 126.9, 127.3, 128.0, 128.6, 128.8, 132.2, 135.4, 136.2, 137.7, 141.5 and 150.1. IR (KBr, ν): 2923, 1490, 1461, 1314, 1179, 1010, 828, 741 and 719 cm^{-1}. EI-MS (*m/z*, rel. int., %): 494 (1, M^+), 149 (16), 130 (11), 129 (11), 123 (11), 111 (13), 97 (25), 81 (56) and 69 (100). HRMS (ESI–TOF, *m/z*): Found 495.1178; $C_{28}H_{24}BrN_4$ $(M+H)^+$ requires 495.1184.

1-((5-(2-(1*H*-Indol-1-yl)ethyl)-1-(4-chlorophenyl)-1*H*-pyrazol-3-yl) methyl)-1*H*-indole (5c)

Orange waxy solid; yield: 53%. ^{1}H NMR (400 MHz) δ: 2.99 (t, *J* = 7.0, 2H), 4.14 (t, *J* = 7.0, 2H), 5.31 (s, 2H), 5.92 (s, 1H), 6.34 (dd, *J* = 3.2 and *J* = 0.8, 1H), 6.55 (dd, *J* = 3.2 and *J* = 0.8, 1H), 6.67 (d, *J* = 3.1, 1H), 6.89-6.93 (m, 2H), 7.06-7.08 (m, 2H), 7.11-7.15 (m, 2H), 7.19 (d, *J* = 3.2, 1H), 7.20-7.24 (m, 3H), 7.44 (d, *J* = 8.2, 1H), 7.55-7.57 (m, 1H) and 7.64-7.67 (m, 1H). ^{13}C NMR (100 MHz) δ: 26.9, 44.2, 45.8, 101.7, 101.8, 104.9, 108.7, 109.7, 119.6, 119.6, 121.0, 121.1, 121.7, 121.7, 126.7, 127.4, 128.0, 128.7, 128.8, 129.2, 134.2, 135.4, 136.2, 137.3, 141.6 and 150.1. IR (KBr, ν): 2926, 2854, 1495, 1461, 1313, 1180, 1091, 1011, 833 and 7429 cm^{-1}. EI-MS (*m/z*, rel. int., %): 450 (11, M^+), 144 (16), 139 (11), 90 (97), 127 (39), 111 (26), 83 (32) and 43 (100). HRMS (ESI–TOF, *m/z*): Found 451.1690; $C_{28}H_{24}ClN_4$ $(M+H)^+$ requires 451.1689.

1-((5-(2-(1*H*-Indol-1-yl)ethyl)-1-*p*-tolyl-1*H*-pyrazol-3-yl) methyl)-1*H*-indole (5d)

Orange waxy solid; yield: 62%. ^{1}H NMR (400 MHz) δ: 2.37 (s, 3H), 2.99 (t, *J* = 7.4, 2H), 4.11 (t, *J* = 7.4, 2H), 5.31 (s, 2H), 5.87 (s, 1H), 6.35 (dd, *J* = 3.2 and *J* = 0.9, 1H), 6.54 (dd, *J* = 3.2 and *J* = 0.9, 1H), 6.73 (d, *J* = 3.2, 1H), 6.89-6.92 (m, 1H), 7.01-7.06 (m, 4H), 7.12-7.16 (m, 4H), 7.18 (d, *J* = 3.2, 1H), 7.44-7.46 (m, 1H), 7.54-7.57 (m, 1H) and 7.63-7.66 (m, 1H). ^{13}C NMR (100 MHz) δ: 21.1, 27.1, 44.3, 45.5, 101.6, 101.6, 104.5, 108.8, 109.8, 119.4, 119.5, 120.9, 121.0, 121.5, 121.6, 125.5, 127.4, 128.0, 128.7, 128.8, 129.8, 136.3, 136.6, 138.5, 138.5, 141.2 and 149.5. IR (KBr, ν): 2919, 2851, 1612, 1518, 1484, 1463, 1388, 1314, 1181, 1014, 824, 763 and 741 cm^{-1}. EI-MS (*m/z*, rel. int., %): 431 (23, $[M+1]^+$), 430 (61, M^+), 314 (15), 183 (17), 169 (11), 130 (100), 103 (12), 91 (11) and 77 (12). HRMS (ESI–TOF, *m/z*): Found 453.2088; $C_{29}H_{26}N_4Na$ $(M+Na)^+$ requires 453.2055.

5-Methoxy-1-((5-(2-(5-methoxy-1*H*-indol-1-yl)ethyl)-1-phenyl -1*H*-pyrazol-3-yl)methyl)-1*H*-indole (5e)

Beige waxy solid; yield: 65%. ^{1}H NMR (400 MHz) δ: 2.99 (t, *J* = 7.3, 2H), 3.82 (s, 3H), 3.85 (s, 3H), 4.09 (t, *J* = 7.3, 2H), 5.28 (s, 2H), 5.88 (s, 1H), 6.28 (d, *J* = 3.0, 1H), 6.47 (d, *J* = 3.0, 1H), 6.70 (d, *J* = 3.0, 1H), 6.71-6.74 (m, 2H), 6.79 (d, *J* = 8.9, 1H), 6.89 (dd, *J* = 8.9 and *J* = 2.4, 1H), 7.03 (d, *J* = 2.2, 1H), 7.11-7.13 (m, 2H), 7.15 (d, *J* = 3.0, 1H) and 7.31-7.36 (m, 4H). ^{13}C NMR (100 MHz) δ: 27.0, 44.3, 45.6, 55.8, 101.1, 101.1, 102.6, 102.6, 104.6, 109.5, 110.5, 111.9, 111.9, 125.5, 127.9, 128.3, 128.6, 128.9, 129.1, 129.2, 130.7, 131.5, 138.8, 141.3, 149.6, 154.0 and 154.1. IR (KBr, ν): 2934, 2831, 1620, 1598, 1502, 1486, 1449, 1238, 1150, 1029, 799, 753 and 719 cm^{-1}. EI-MS (*m/z*, rel. int., %): 477 (11, $[M+1]^+$), 476 (31, M^+), 160 (100), 117 (26), 77 (11) and 43 (13). HRMS (ESI–TOF, *m/z*): Found 477.2292; $C_{30}H_{29}N_4O_2$ $(M+H)^+$ requires 477.2291.

5-Bromo-1-((5-(2-(5-bromo-1*H*-indol-1-yl)ethyl)-1-phenyl-1*H*-pyrazol-3-yl)methyl)-1*H*-indole (5f)

Beige solid, m.p.: 146-148 °C; yield: 69%. ^{1}H NMR (400 MHz) δ: 2.99 (t, *J* = 7.1, 2H), 4.07 (t, *J* = 7.1, 2H), 5.26 (s, 2H), 5.80 (s, 1H), 6.25 (d, *J* = 3.1, 1H), 6.47 (d, *J* = 3.1, 1H), 6.66 (d, *J* = 3.1, 1H), 6.69 (d, *J* = 8.7, 1H), 6.72-6.74 (m, 2H), 7.05-7.10 (m, 3H), 7.15 (d, *J* = 3.1, 1H), 7.27-7.28 (m, 1H), 7.33-7.35 (m, 2H), 7.67 (d, *J* = 1.8, 1H) and 7.76-7.77 (m, 1H). ^{13}C NMR (100 MHz) δ: 26.9, 44.4, 45.7, 101.2, 101.3, 104.6, 110.2, 111.2, 112.8, 112.9, 123.4, 123.5, 124.4, 124.5, 125.5, 128.5, 128.5, 129.2, 129.3, 130.2, 130.5, 134.1, 134.8, 138.8, 141.1 and 149.2. IR (KBr, ν): 2924, 1734, 1598, 1505, 1469, 1275, 1255, 1193, 869, 793, 752, 719 and 696 cm^{-1}. EI-MS (*m/z*, rel. int., %): 574 (10, M^+), 495 (54), 483 (54), 209 (97), 208 (100), 169 (42), 141 (17), 129 (79), 102 (24) and 77 (37). Anal. Calc.: C, 58.56; H, 3.86; N, 9.76. Found: C, 58.57; H, 4.03; N, 9.72.

9-((5-(2-(9*H*-Carbazol-9-yl)ethyl)-1-phenyl-1*H*-pyrazol-3-yl) methyl)-9*H*-carbazole (5g)

Beige solid, m.p.: 182-184 °C; yield: 72%. ^{1}H NMR (400 MHz) δ: 2.96 (t, *J* = 7.5, 2H), 4.12 (t, *J* = 7.5, 2H), 5.50 (s, 2H), 5.88 (s, 1H), 6.81 (d, *J* = 8.1, 2H), 7.08-7.13 (m, 4 H), 7.18-7.22 (m, 3H), 7.25-7.30 (m, 4H), 7.47-7.51 (m, 2H), 7.55 (d, *J* = 8.1, 2H), 7.94 (d, *J* = 7.7, 2H) and 8.13 (d, *J* = 7.7, 2H). ^{13}C NMR (100 MHz) δ: 25.2, 40.9, 42.1, 104.8, 108.0, 109.0, 119.0, 119.2, 120.2, 120.3,

122.9, 123.1, 125.5, 125.6, 125.8, 128.2, 129.2, 138.9, 139.6, 140.5, 141.4 and 149.4. IR (KBr, ν): 2936, 1734, 1626, 1597, 1501, 1485, 1453, 1326, 1235, 1153, 776, 749, 721 and 693 cm^{-1}. EI-MS (*m/z*, rel. int., %): 517 (9, $[M+1]^+$), 516 (23, M^+), 181 (15), 180 (100), 152 (9) and 77 (6). HRMS (ESI–TOF, *m/z*): Found 517.2389; $C_{36}H_{29}N_4$ $(M+H)^+$ requires 517.2392.

1-((5-Benzyl-1-phenyl-1*H*-pyrazol-3-yl)methyl)-1*H*-indole (6a)

Yellow oil; yield: 73%. ^1H NMR (400 MHz) δ: 3.87 (s, 2H), 5.32 (s, 2H), 5.89 (s, 1H), 6.51 (dd, *J* = 3.1 and *J* = 0.7, 1H), 6.97-6.99 (m, 2H), 7.08-7.12 (m, 1H), 7.16-7.22 (m, 5H), 7.33-7.41 (m, 5H), 7.47 (d, *J* = 8.3, 1H) and 7.62 (d, *J* = 7.8, 1H). ^{13}C NMR (100 MHz) δ: 32.4, 44.3, 101.5, 105.9, 109.8, 119.4, 120.8, 121.5, 125.6, 126.6, 128.0, 128.2, 128.4, 128.5, 128.7, 129.1, 136.3, 137.7, 139.4, 143.5 and 149.4. IR (film, ν): 2921, 1598, 1501, 1461, 1385, 1313, 1182, 1016, 761, 742 and 696 cm^{-1}. EI-MS (*m/z*, rel. int., %): 364 (15, $[M+1]^+$), 363 (52, M^+), 247 (100), 207 (15), 115 (10), 91 (51) and 77 (28). HRMS (ESI–TOF, *m/z*): Found 364.1811; $C_{25}H_{22}N_3$ $(M+H)^+$ requires 364.1814.

1-((5-Benzyl-1-(4-bromophenyl)-1*H*-pyrazol-3-yl)methyl)-1*H*-indole (6b)

Yellow oil; yield: 57%. ^1H NMR (400 MHz) δ: 3.86 (s, 2H), 5.31 (s, 2H), 5.91 (s, 1H), 6.52 (dd, *J* = 3.2 and *J* = 0.6, 1H), 6.97-6.99 (m, 2H), 7.08-7.12 (m, 1H), 7.18-7.22 (m, 7H), 7.45 (d, *J* = 8.2, 1H), 7.52 (d, *J* = 8.7, 2H) and 7.62 (d, *J* = 7.8, 1H). ^{13}C NMR (100 MHz) δ: 32.3, 44.1, 101.6, 106.5, 109.7, 119.5, 120.9, 121.6, 121.9, 126.7, 126.9, 128.0, 128.3, 128.6, 128.7, 132.2, 136.2, 137.4, 138.4, 143.4 and 149.7. IR (film, ν): 2919, 1733, 1494, 1461, 1382, 1312, 1180, 1070, 1009, 831, 742, 704 and 670 cm^{-1}. EI-MS (*m/z*, rel. int., %): 443 (72, $[M+2]^+$), 441 (71, M^+), 328 (21), 325 (100), 246 (31), 169 (24), 155 (29), 130 (32), 115 (22), 91 (77) and 77 (33). HRMS (ESI–TOF, *m/z*): Found 442.0909; $C_{25}H_{21}BrN_3$ $(M+H)^+$ requires 442.0919.

1-((5-Benzyl-1-(4-chlorophenyl)-1*H*-pyrazol-3-yl)methyl)-1*H*-indole (6c)

Brown waxy solid; yield: 50%. ^1H NMR (400 MHz) δ: 3.87 (s, 2H), 5.32 (s, 2H), 5.91 (s, 1H), 6.52 (dd, *J* = 3.2 and *J* = 0.8, 1H), 6.97-6.99 (m, 2H), 7.08-7.12 (m, 1H), 7.18-7.28 (m, 7H), 7.38 (d, *J* = 8.8, 2H), 7.46 (d, *J* = 8.2, 1H) and 7.63 (d, *J* = 7.7, 1H). ^{13}C NMR (100 MHz) δ: 32.3, 44.2, 101.7, 106.4, 109.7, 119.5, 120.9, 121.6, 126.7, 126.7, 128.0, 128.3, 128.6, 128.7, 129.3, 134.0, 136.2, 137.4, 137.9, 143.5 and 149.7. IR (KBr, ν): 2924, 1725, 1597, 1498, 1463, 1383, 1312, 1180, 1092, 1011, 835, 742, 706 and 670 cm^{-1}. EI-MS (*m/z*, rel. int., %): 399 (25, $[M+2]^+$), 397 (69, M^+), 283 (34), 281 (100), 130 (15), 111 (15), 91 (40) and 77 (11). HRMS (ESI–TOF, *m/z*): Found 398.1431; $C_{25}H_{21}ClN_3$ $(M+H)^+$ requires 398.1424.

1-((5-Benzyl-1-*p*-tolyl-1*H*-pyrazol-3-yl)methyl)-1*H*-indole (6d)

Yellow oil; yield: 70%. ^1H NMR (400 MHz) δ: 2.39 (s, 3H), 3.85 (s, 2H), 5.31 (s, 2H), 5.87 (s, 1H), 6.51 (dd, *J* = 3.1 and *J* = 0.6, 1H), 6.97-6.99 (m, 2H), 7.07-7.11 (m, 1H), 7.17-7.22 (m, 9H), 7.47 (d, *J* = 8.2, 1H) and 7.62 (d, *J* = 7.9, 1H). ^{13}C NMR (100 MHz) δ: 21.1, 32.3, 44.3, 101.5, 105.6, 109.8, 119.4, 120.8, 121.5, 125.4, 126.6, 128.0, 128.4, 128.5, 128.7, 129.7, 136.2, 136.9, 137.9, 138.2, 143.5 and 149.1 IR (film, ν): 2920, 1612, 1612, 1543, 1517, 1461, 1386, 1313, 1182, 1014, 826, 742 and 710 cm^{-1}. EI-MS (*m/z*, rel. int., %): 378 (15, $[M+1]^+$), 377 (49, M^+), 262 (21), 261 (100), 130 (12), 91 (53), 69 (12) and 43 (12). HRMS (ESI–TOF, *m/z*): Found 378.1964; $C_{26}H_{24}N_3$ $(M+H)^+$ requires 378.1970.

1-((5-Benzyl-1-phenyl-1*H*-pyrazol-3-yl)methyl)-5-methoxy-1*H*-indole (6e)

Brown oil; yield: 65%. ^1H NMR (400 MHz) δ: 3.83 (s, 3H), 3.87 (s, 2H), 5.28 (s, 2H), 5.88 (s, 1H), 6.43 (dd, *J* = 3.1 and *J* = 0.8, 1H), 6.86 (dd, *J* = 8.9 and *J* = 2.5, 1H), 6.97-7.00 (m, 2H), 7.09 (d, *J* = 2.5, 1H), 7.16-7.22 (m, 4H) and 7.32-7.41 (m, 6H). ^{13}C NMR (100 MHz) δ: 32.4, 44.5, 55.8, 101.0, 102.6, 105.9, 110.5, 111.8, 125.5, 126.6, 128.1, 128.4, 128.5, 128.6, 129.1, 129.1, 131.6, 137.7, 139.4, 143.4, 149.4 and 154.1. IR (film, ν): 2933, 1726, 1598, 1500, 1486, 1449, 1384, 1237, 1150, 1030, 798, 763 and 696 cm^{-1}. EI-MS (*m/z*, rel. int., %): 394 (24, $[M+1]^+$), 393 (80, M^+), 248 (20), 247 (100), 117 (11), 91 (60) and 77 (31). HRMS (ESI–TOF, *m/z*): Found 394.1925; $C_{26}H_{24}N_3O$ $(M+H)^+$ requires 394.1919.

5-Bromo-1-((5-(4-methylbenzyl)-1-phenyl-1*H*-pyrazol-3-yl) methyl)-1*H*-indole (6f)

Brown oil; yield: 61%. ^1H NMR (400 MHz) δ: 2.28 (s, 3H), 3.83 (s, 2H), 5.27 (s, 2H), 5.84 (s, 1H), 6.43 (dd, *J* = 3.2 and *J* = 0.7, 1H), 6.88 (d, *J* = 7.9, 2H), 7.02 (d, *J* = 7.9, 2H), 7.19 (d, *J* = 3.2, 1H), 7.27 (d, *J* = 1.9, 1H), 7.31-7.42 (m, 6H) and 7.73 (d, *J* = 1.9, 1H). ^{13}C NMR (100 MHz) δ: 21.0, 32.0, 44.5, 101.1, 105.7, 111.3, 112.8, 123.3, 124.3, 125.5, 128.2, 128.3, 129.1, 129.2, 129.3, 130.4, 134.6, 134.9, 136.2, 139.4, 144.0 and 148.7. IR (film, ν): 2920, 1732, 1598, 1503, 1466, 1442, 1383, 1186, 1016, 792, 756, 720 and 694 cm^{-1}. EI-MS (*m/z*, rel. int., %): 457 (26, $[M+2]^+$), 455 (26, M^+), 262 (21), 261 (100), 169 (10), 105 (30) and 77 (27). HRMS (ESI–TOF, *m/z*): Found 456.1079; $C_{26}H_{23}BrN_3$ $(M+H)^+$ requires 456.1075.

9-((5-Benzyl-1-phenyl-1*H*-pyrazol-3-yl)methyl)-9*H*-carbazole (6g)

Beige waxy solid; yield: 71%. ^1H NMR (400 MHz) δ: 3.79 (s, 2H), 5.51 (s, 2H), 5.83 (s, 1H), 6.88-6.91 (m, 2H), 7.11-7.14 (m, 2H), 7.20-7.24 (m, 3H), 7.30-7.39 (m, 4H), 7.42-7.46 (m, 3H), 7.56 (d, *J* = 8.2, 2H) and 8.08 (d, *J* = 7.7. 2H). ^{13}C NMR (100 MHz) δ: 32.2, 41.0, 105.7, 109.1, 119.1, 120.2, 123.0, 125.6, 125.7, 126.5, 128.1, 128.3, 128.5, 129.1, 137.7, 139.3, 140.5, 143.4 and 149.2. IR (KBr, ν): 2920, 1589, 1493, 1460, 1382, 1309, 1179, 1069, 1008, 830, 742 and 702 cm^{-1}. EI-MS (*m/z*, rel. int., %): 414 (23, $[M+1]^+$), 413 (67, M^+), 248 (20), 247 (100), 180 (8), 115 (7), 91 (46) and 77 (24). HRMS (ESI–TOF, *m/z*): Found 436.1810; $C_{29}H_{23}N_3Na$ $(M+Na)^+$ requires 436.1790.

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