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A novel allylic substitution strategy to four-component synthesis of pyrazole-substituted fused pyrroles

Xing-Chao Tu, Wei Fan, Bo Jiang *, Shu-Liang Wang, Shu-Jiang Tu *

School of Chemistry and Chemical Engineering, and Jiangsu Key Laboratory of Green Synthetic Chemistry for Functional Materials, Jiangsu Normal University, Xuzhou 221116, Jiangsu, PR China

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ABSTRACT

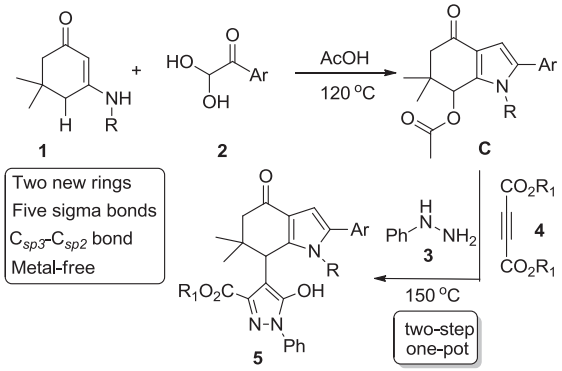
The selective formation of pyrazole-substituted fused pyrroles through HOAc-mediated multicomponent reactions of enaminones with arylglyoxal monohydrates and generated in situ pyrazole-3-carboxylates was developed. It constructed a variety of bis-heterocyclic pairs under mild conditions in a domino process. Reaction driving tandem cyclization/allylic esterification/allylic substitution was achieved through the formation of in situ generation of allyl esters and pyrazole-3-carboxylates from readily available starting materials. Up to two new five-membered heterocyclic rings and five new sigma bonds including a C(sp3)–C(sp2) bond were formed in a single reaction without isolated intermediates.

1. Introduction

The direct and selective allylic substitution with carbon nucleophiles constitutes one of the most important and useful carbon–carbon bond-forming reactions in organic synthesis, and a variety of transition metal complexes have been explored as catalysts for this regio- and stereoselective reactions.[1,2] Thus, the design of new allylic substitution generated in situ, especially those of metal-free conditions, remains challenging, and continues to attract interest to synthetic community.

Fused pyrroles are common structural motifs in many biologically active molecules and pharmaceutical substances.[3] Owing to their biological importance, these derivatives attract the attention of synthetic chemists. In the past several decades, many methodologies for the synthesis of fused pyrroles have been developed, which involved cycloketone annulations,[4] rearrangement-cyclization of alkynol,[5a] alkynyl ketones,[5b] metal-catalyzed cascade cyclization of alkynes,[6] and 1,3-dipolar cycloadditions of münchnone derivatives.[7] Despite these limited construction of fused pyrroles, an exploration of a versatile strategy for the direct formation of fused pyrrole framework would be highly favorable. To our best of knowledge, the utilization of allylic substitution generated in situ combined with multicomponent domino reactions (MDRs)[8] for the construction of pyrazole-substituted fused pyrrole skeleton has not been published so far.

Recently, we have been engaging in the development of unique MDRs that can provide easy access to new core structures of chemical and pharmaceutical interest.[9] During our study of this topic, we now discovered a novel Brønsted acid-promoted multicomponent N-heteroannulations of enaminones **1** with arylglyoxal monohydrates **2**, phenylhydrazine **3**, and acetylenedicarboxylates **4** selectively providing multifunctionalized fused pyrrole derivatives through the control of charging sequence (Scheme 1). The great features of the present domino strategy are shown by the fact that the construction of two new rings including pyrrole and pyrazole rings and five new sigma bonds formation containing the direct C(sp^3)–C(sp^2) bond were readily achieved via Brønsted



Scheme 1. The domino synthesis of fused pyrroles **5**.

* Corresponding authors. Tel./fax: +86 516 83500065; e-mail addresses: jiangchem@jsnu.edu.cn (B. Jiang), laotu@jsnu.edu.cn (S.-J. Tu).

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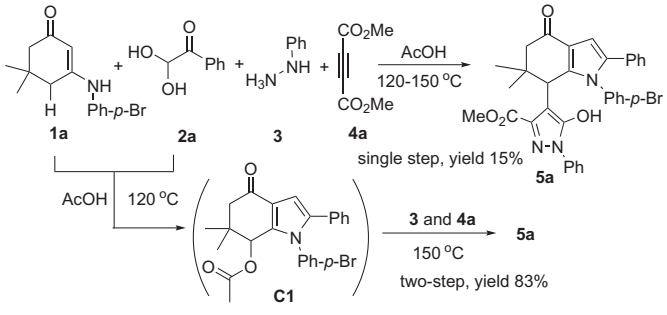
acid-mediated domino reaction, and allylic substitution generated in situ occurred in a one-pot operation. The present work represents the special examples for synthesizing such important types of bis-heterocyclic pairs containing pyrazole and pyrrole motifs.

2. Results and discussion

We have planned to link two biologically important nuclei, pyrazoles and fused pyrroles, to generate a new set of compounds, pyrazole-substituted fused pyrroles, using allylic substitution-based heterocyclization of enaminones **1** with arylglyoxal monohydrates **2**, phenylhydrazine **3**, and acetylenedicarboxylates **4**. Here, it should be mentioned that the chemistry of enaminones, consisting of 1,3-bisnucleophilic centers, has a wide application on the synthesis of heterocyclic compounds.[9a,b,10] We previously developed a new three-component domino reaction of enaminones for the synthesis of multifunctionalized fused pyrroles **C** through allylic esterification.[9a] So, we reasoned that new type of allylic substitution could be achieved under suitable reaction conditions using allyl esters **C** generated in situ as allylating agents and pyrazole-3-carboxylates generated in situ as carbon nucleophiles in one-pot operation, based on the success of allylic substitution between allyl esters and carbon nucleophiles.[2]

With this notion in mind, we started this study by subjecting a preformed 3-((4-bromophenyl)amino)-5,5-dimethylcyclo-hex-2-enone **1a** and phenylglyoxal monohydrate **2a** to the reaction with phenylhydrazine **3** and dimethyl acetylenedicarboxylate **4a** (DMAD) in HOAc under microwave heating conditions (Scheme 2). As we expected, pyrazole-substituted fused pyrroles **5a** with 15% chemical yield was sustained, supported by NMR analysis and X-ray diffraction of single crystal **5a** (Fig. 1). In further steps, possible options were considered to improve yield of expected product **5a**. (a) Charging sequence. The mixture of enaminones **1a** and glyoxal monohydrate **2a** in HOAc was firstly heated at 120 °C for 10 min under microwave irradiation, and then phenylhydrazine **3** and dimethyl acetylenedicarboxylate **4a** (DMAD) were added into the mixed system at 150 °C for 15 min. The product **5a** was obtained in 83% isolated yield by flash chromatography (Table 1, entry 5). (b) Acidic solvents. Both HCOOH and propionic acid were used within the same experimental procedures. The product **5a** was not observed in HCOOH while the propionic acid gave the 61% yield of **5a**. Also, HOAc was chosen for further study. It turned out that in this reaction acetic acid behaves as nucleophile, reaction media, and Brønsted acid promoter for the allylic pyrazolization simultaneously.



Scheme 2. The optimized synthesis of fused pyrroles **5a**.

With the optimized multicomponent protocol in hand, we next set out to explore its scope using various readily available starting materials. The reactions of various arylglyoxal monohydrates **1** with *N*-substituted 3-aminocyclohex-2-enones (**2a**–**f**) in acetic acid were performed for a short period, following with addition of both phenylhydrazine **3** and dimethyl acetylenedicarboxylate **4a** were added into the mixed system under the conditions described above (25–32 min). The results are summarized in Table 1. Obviously, not only *N*-aryl enaminones **1a**–**c**, which possess electron-withdrawing

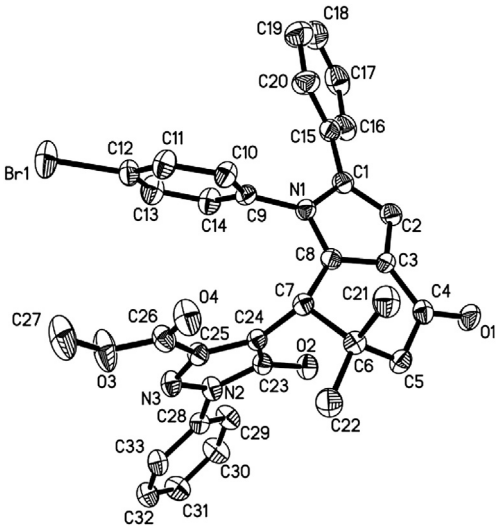


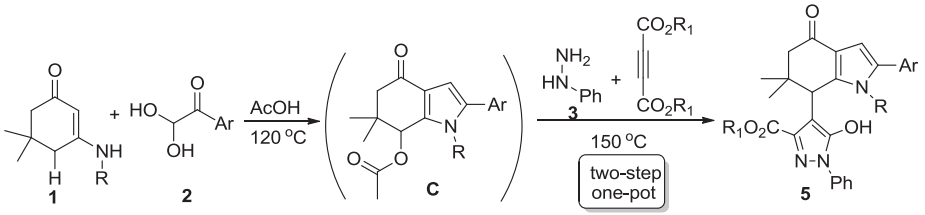
Fig. 1. X-ray structure of **5a**.[11]

substituents, such as fluoro, bromo, and chloro groups at the para position of the benzene ring, but also **1d**–**e** having electron-donating substituents, such as methyl and methoxy groups produced the corresponding pyrazole-substituted fused pyrroles **5** in good to high yields, respectively. Both electron-deficient and electron-rich groups on the arylglyoxal monohydrates were suitable for the multicomponent domino reactions. Similarly, the diethyl acetylenedicarboxylate **4b** was another appropriate partner in the multicomponent domino reactions and worked well, providing the corresponding products **5** in good yields of 77–85%. With no exceptions, the reaction of secondary allylic acetates with different substitution patterns resulted in the direct displacement of the acetoxy group with pyrazole-3-carboxylates generated in situ. The results exhibit the scope and generality of the novel allylic substitution-based multicomponent domino reaction with respect to a range of enaminones and arylglyoxal monohydrate substrates, although 5,5-unsubstituted enaminones failed to take place in allylic substitution with pyrazole-3-carboxylates since it was converted into the polysubstituted bis-indoles.[9a]

In all cases, the complexity of resulting products from this new reaction illustrates the remarkable regioselectivity of the sequence starting from very common and easily accessible inexpensive starting materials. In general, the reaction occurred at a very fast speed with all cases finished within 25–32 min. Water and alcohols were formed as the major by-products, which make the work-up convenient. In most cases, the products can precipitate out after cold water was poured into the reaction mixture. During these domino processes, up to two new rings (pyrrole and pyrazole rings) and five new sigma bonds including a C(sp^3)–C(sp^2) bond were formed accompanied by cleavage of one C=O and three C–O bonds of the arylglyoxal monohydrates and acetylenedicarboxylates, and direct allylic pyrazolation of fused pyrroles **C** was simultaneously achieved via intermolecular allylic substitution between allyl esters **C** and pyrazole-3-carboxylates **E**;[12] both of them were generated in situ (Table 1). This observation is very interesting and useful in organic chemistry.

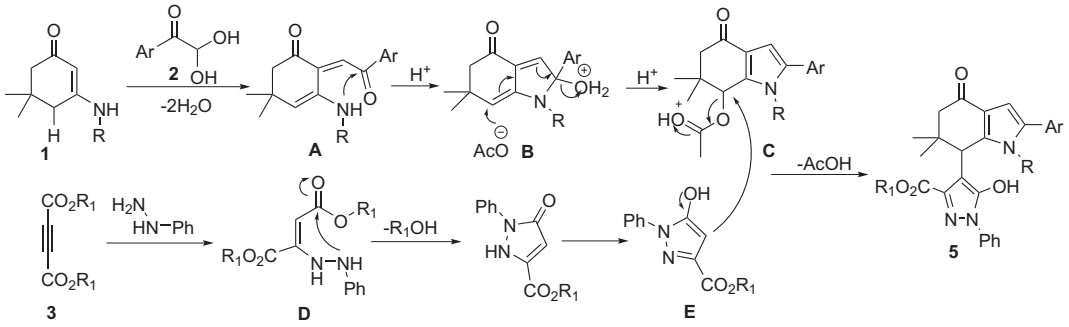
The mechanism for formation of products **5** was proposed and shown in Scheme 3. The reaction involves the domino cyclization to give allylic acetates **C**,[9a] which is followed by subsequent intermolecular nucleophilic substitution with pyrazole-3-carboxylates **E**,[12] derived from phenylhydrazine **3** and acetylenedicarboxylates **4**, yielding final products **5**. This mechanism was supported by the fact that the isolated allylic acetates **C1** was employed to subject with isolated pyrazole-3-carboxylates **E** in HOAc, generating pyrroles **5a** in 82% yield (Scheme 4).

Table 1
Multicomponent domino synthesis of pyrazole-substituted fused pyrroles **5**

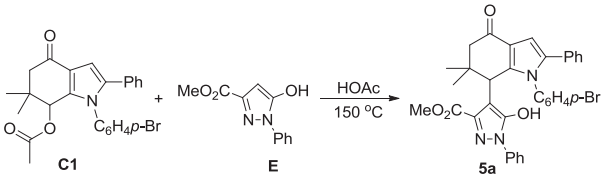


Entry	5	R	Ar	R_1	Time[a]/min	Yield[b] (%)
1	**5a**	*p*-BrC_6H_4 (**1a**)	C_6H_5 (**2a**)	Me (**4a**)	25	83
2	**5b**	*p*-BrC_6H_4 (**1a**)	*p*-ClC_6H_4 (**2b**)	Me (**4a**)	27	84
3	**5c**	*p*-BrC_6H_4 (**1a**)	*p*-BrC_6H_4 (**2c**)	Me (**4a**)	26	87
4	**5d**	*p*-BrC_6H_4 (**1a**)	*p*-$CH_3C_6H_4$ (**2d**)	Me (**4a**)	29	88
5	**5e**	*p*-BrC_6H_4 (**1a**)	C_6H_5 (**2a**)	Et (**4b**)	28	82
6	**5f**	*p*-BrC_6H_4 (**1a**)	*p*-ClC_6H_4 (**2b**)	Et (**4b**)	31	81
7	**5g**	*p*-BrC_6H_4 (**1a**)	*p*-BrC_6H_4 (**2c**)	Et (**4b**)	27	85
8	**5h**	*p*-FC_6H_4 (**1b**)	C_6H_5 (**2a**)	Me (**4a**)	25	83
9	**5i**	*p*-FC_6H_4 (**1b**)	*p*-ClC_6H_4 (**2b**)	Me (**4a**)	29	86
10	**5j**	*p*-FC_6H_4 (**1b**)	*p*-BrC_6H_4 (**2c**)	Me (**4a**)	27	87
11	**5k**	*p*-FC_6H_4 (**1b**)	*p*-$CH_3C_6H_4$ (**2d**)	Me (**4a**)	30	89
12	**5l**	*p*-FC_6H_4 (**1b**)	*p*-BrC_6H_4 (**2c**)	Et (**4b**)	31	84
13	**5m**	*p*-ClC_6H_4 (**1c**)	C_6H_5 (**2a**)	Me (**4a**)	29	79
14	**5n**	*p*-ClC_6H_4 (**1c**)	*p*-ClC_6H_4 (**2b**)	Me (**4a**)	25	85
15	**5o**	*p*-ClC_6H_4 (**1c**)	*p*-BrC_6H_4 (**2c**)	Me (**4a**)	27	83
16	**5p**	*p*-ClC_6H_4 (**1c**)	*p*-$CH_3C_6H_4$ (**2d**)	Me (**4a**)	28	81
17	**5q**	*p*-ClC_6H_4 (**1c**)	*p*-ClC_6H_4 (**2b**)	Et (**4b**)	32	87
18	**5r**	*p*-ClC_6H_4 (**1c**)	*p*-BrC_6H_4 (**2c**)	Et (**4b**)	28	86
19	**5s**	*p*-$CH_3C_6H_4$ (**1d**)	C_6H_5 (**2a**)	Me (**4a**)	27	78
20	**5t**	*p*-$CH_3C_6H_4$ (**1d**)	*p*-ClC_6H_4 (**2b**)	Me (**4a**)	25	87
21	**5u**	*p*-$CH_3C_6H_4$ (**1d**)	*p*-BrC_6H_4 (**2c**)	Me (**4a**)	26	86
22	**5v**	*p*-$CH_3C_6H_4$ (**1d**)	*p*-$CH_3C_6H_4$ (**2d**)	Me (**4a**)	27	82
23	**5w**	*p*-$CH_3C_6H_4$ (**1d**)	*p*-ClC_6H_4 (**2b**)	Et (**4b**)	29	83
24	**5x**	*p*-$CH_3C_6H_4$ (**1e**)	C_6H_5 (**2a**)	Me (**4a**)	25	79
25	**5y**	*p*-$CH_3C_6H_4$ (**1e**)	*p*-ClC_6H_4 (**2b**)	Me (**4a**)	28	86
26	**5z**	*p*-$CH_3C_6H_4$ (**1e**)	*p*-BrC_6H_4 (**2c**)	Me (**4a**)	26	89
27	**5aa**	*p*-$CH_3C_6H_4$ (**1e**)	*p*-$CH_3C_6H_4$ (**2d**)	Me (**4a**)	28	78
28	**5ab**	*p*-$CH_3C_6H_4$ (**1e**)	C_6H_5 (**2a**)	Et (**4b**)	29	77
29	**5ac**	*p*-$CH_3C_6H_4$ (**1e**)	*p*-$CH_3C_6H_4$ (**2d**)	Et (**4b**)	32	81

[a] Total reaction time of two steps.
[b] Isolated yield.



Scheme 3. The proposed mechanism for the formations of fused pyrroles **5**.



Scheme 4. The supporting reaction for the proposed mechanism.

3. Conclusion

In conclusion, we have developed HOAc-mediated multicomponent reactions that enable metal-free allylic substitution of in situ generation of both pyrazole-3-carboxylates and allyl esters. This domino strategy provides a facile and efficient method for construction of structurally diverse bis-heterocyclic pairs containing pyrazole and pyrrole motifs. Notable features of these reactions

include short reaction times, convenient one-pot operation, high regioselectivity, and atom-economical process with a broad range of starting materials. Future work will focus on an expansion of the reaction's scope and on the use of this methodology in its asymmetric version.

4. Experimental section

4.1. General

Microwave irradiation was carried out with Initiator 2.5 Microwave Synthesizers from Biotage, Uppsala, Sweden. Melting points were determined in open capillaries and were uncorrected. IR spectra were taken on a FT-IR-Tensor 27 spectrometer in KBr pellets and reported in cm^{-1}. ^1H NMR spectra were measured on a Bruker DPX 400 MHz spectrometer in DMSO-d_6 with chemical shift (δ) given in parts per million relative to TMS as internal standard [(s=singlet, d=doublet, t=triplet, br s=broad singlet, m=multiplet), coupling constant (Hertz)]. HRMS (ESI) was determined by using microTOF-Q II HRMS/MS instrument (BRUKER). X-ray crystallographic analysis was performed with a Siemens P4 diffractometer.

4.2. Typical procedure for the preparation of 5

In a 10-mL reaction vial, enaminones (**1**, 1 mmol, 1.0 equiv), phenylglyoxal monohydrates (**2**, 1 mmol, 1.0 equiv), and acetic acid (2.0 mL) were mixed equally and then heated to 120 °C for 10–12 min under microwave irradiation. Acetylenedicarboxylates (**4**, 1.0 mmol, 1.0 equiv) was then added into the mixture system, and phenylhydrazine (**3**, 1.0 mmol, 1.0 equiv) was filled slowly (within 2 min) under constantly stirring conditions. The reaction temperature was raised to 150 °C for 15–18 min under microwave irradiation. Upon completion as shown by TLC monitoring, the reaction mixture diluted with cold water. The resulting mixture was purified by flash column chromatography on silica gel (*n*-hexane/diethyl ether=7/1) to give the desired product **5**.

4.3. Methyl 4-(1-(4-bromophenyl)-4,5,6,7-tetrahydro-6,6-dimethyl-4-oxo-2-phenyl-1*H*-indol-7-yl)-5-hydroxy-1-phenyl-1*H*-pyr-azole-3-carboxylate (5a)

White solid, mp: 269–271 °C.

IR (KBr, ν, cm^{-1}): 2955, 1719, 1709, 1622, 1598, 1575, 1491, 1395, 1218, 1172, 1044, 1015, 958, 830, 808, 756. ^1H NMR (400 MHz, DMSO-d_6) δ: 10.04 (s, 1H, OH), 7.62 (d, J=7.2 Hz, 1H, Ar–H), 7.55 (d, J=8.0 Hz, 2H, Ar–H), 7.48 (t, J=7.6 Hz, 2H), 7.45–7.36 (m, 2H, Ar–H), 7.26–7.17 (m, 3H, Ar–H), 7.17–7.10 (m, 3H, Ar–H), 6.67 (s, 1H, Ar–H), 6.40 (d, J=7.4 Hz, 1H, Ar–H), 4.55 (s, 1H, CH), 3.71 (s, 3H, CH_3), 2.85 (d, J=16.0 Hz, 1H, CH_2), 2.09 (d, J=5.4 Hz, 1H, CH_2), 1.24 (s, 3H, CH_3), 0.87 (s, 3H, CH_3). HRMS (ESI) m/z: calcd for $C_{33}H_{28}BrN_3O_4$: 608.1185 $[M-H]^-$; found: 608.1153.

4.4. Methyl 4-(1-(4-bromophenyl)-2-(4-chlorophenyl)-4,5,6,7-tetrahydro-6,6-dimethyl-4-oxo-1*H*-indol-7-yl)-5-hydroxy-1-phenyl-1*H*-pyrazole-3-carboxylate (5b)

White solid, mp: 267–269 °C.

IR (KBr, ν, cm^{-1}): 2955, 1719, 1708, 1622, 1596, 1575, 1491, 1469, 1397, 1218, 1172, 1043, 1015, 958, 831, 808, 756, 696. ^1H NMR (400 MHz, $CDCl_3$) δ: 7.69 (d, J=7.6 Hz, 2H, Ar–H), 7.52 (s, 1H, Ar–H), 7.44 (t, J=7.6 Hz, 2H, Ar–H), 7.35 (t, J=7.2 Hz, 1H, Ar–H), 7.26 (s, 1H, Ar–H), 7.10 (d, J=8.4 Hz, 3H, Ar–H), 6.88 (d, J=8.4 Hz, 2H, Ar–H), 6.50 (s, 1H, Ar–H), 6.44 (s, 1H, Ar–H), 4.65 (s, 1H, CH), 3.83 (s, 3H, CH_3), 2.89 (d, J=17.6 Hz, 1H, CH_2), 2.10 (d, J=20.0 Hz, 1H, CH_2), 1.25 (s, 3H, CH_3), 0.97 (s, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$) (δ, ppm): 197.8, 163.0, 149.5, 148.7, 139.7, 137.7, 136.0, 136.0, 133.3, 132.7, 132.1, 129.9, 129.6, 129.4, 129.0, 128.5, 128.0, 123.9, 122.9, 119.6, 106.3, 105.6, 51.9, 48.8, 38.5, 38.1, 28.9, 27.3, 20.6. HRMS (ESI) m/z: calcd for $C_{33}H_{27}BrClN_3O_4$: 642.0795 $[M-H]^-$; found: 642.0794.

4.5. Methyl 4-(1,2-bis(4-bromophenyl)-4,5,6,7-tetrahydro-6,6-dimethyl-4-oxo-1*H*-indol-7-yl)-5-hydroxy-1-phenyl-1*H*-pyra-zole-3-carboxylate (5c)

White solid, mp: 257–259 °C.

IR (KBr, ν, cm^{-1}): 2955, 1720, 1708, 1621, 1575, 1467, 1446, 1402, 1218, 1171, 1043, 1011, 827, 807, 799, 753. ^1H NMR (400 MHz, $CDCl_3$) δ: 7.69 (d, J=7.6 Hz, 2H, Ar–H), 7.52 (s, 1H, Ar–H), 7.44 (t, J=7.6 Hz, 2H, Ar–H), 7.35 (t, J=7.6 Hz, 1H, Ar–H), 7.29–7.22 (m, 3H, Ar–H), 7.09 (s, 1H, Ar–H), 6.81 (d, J=8.4 Hz, 2H, Ar–H), 6.47 (d, 2H, Ar–H), 4.65 (s, 1H, CH), 3.82 (s, 3H, CH_3), 2.89 (d, J=17.6 Hz, 1H, CH_2), 2.10 (d, J=19.2 Hz, 1H, CH_2), 1.25 (s, 3H, CH_3), 0.96 (s, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$) (δ, ppm): 197.9, 163.0, 149.6, 148.8, 139.7, 137.7, 136.0, 136.0, 132.7, 132.1, 131.5, 130.1, 129.9, 129.7, 129.0, 128.0, 124.0, 122.9, 121.5, 119.6, 106.4, 105.6, 51.9, 48.8, 38.5, 38.1, 28.9, 27.3. HRMS (ESI) m/z: calcd for $C_{33}H_{27}Br_2N_3O_4$: 688.0267 $[M-H]^-$; found: 688.0268.

4.6. Methyl 4-(1-(4-bromophenyl)-4,5,6,7-tetrahydro-6,6-dimeth-yl-4-oxo-2-*p*-tolyl-1*H*-indol-7-yl)-5-hydroxy-1-phenyl-1*H*-pyrazole-3-carboxylate (5d)

White solid, mp: 246–247 °C.

IR (KBr, ν, cm^{-1}): 2955, 1716, 1624, 1575, 1492, 1470, 1402, 1285, 1219, 1173, 1121, 1043, 1015, 959, 824, 807, 755, 696. ^1H NMR (400 MHz, $CDCl_3$) δ: 7.70 (d, J=8.0 Hz, 2H, Ar–H), 7.50 (s, 1H, Ar–H), 7.43 (t, J=7.6 Hz, 2H, Ar–H), 7.34 (t, J=7.2 Hz, 1H, Ar–H), 7.24 (s, 1H, Ar–H), 7.11 (s, 1H, Ar–H), 6.91 (d, J=8.0 Hz, 2H, Ar–H), 6.86 (d, J=7.6 Hz, 2H, Ar–H), 6.62–6.43 (m, 2H, Ar–H), 4.65 (s, 1H, CH), 3.83 (s, 3H, CH_3), 2.89 (d, J=17.2 Hz, 1H, CH_2), 2.23 (s, 3H, CH_3), 2.17 (d, J=17.2 Hz, 1H, CH_2), 1.27 (s, 3H, CH_3), 0.98 (s, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$) (δ, ppm): 197.4, 163.0, 149.6, 148.0, 139.7, 137.7, 137.4, 137.0, 136.4, 129.0, 129.0, 128.3, 128.3, 127.8, 123.8, 122.6, 119.6, 106.1, 104.9, 51.9, 48.9, 38.6, 38.1, 28.9, 27.3, 21.2. HRMS (ESI) m/z: calcd for $C_{34}H_{30}BrN_3O_4$: 624.1321 $[M-H]^-$; found: 624.1321.

4.7. Ethyl 4-(1-(4-bromophenyl)-4,5,6,7-tetrahydro-6,6-dimethyl-4-oxo-2-phenyl-1*H*-indol-7-yl)-5-hydroxy-1-phenyl-1*H*-pyrazole-3-carboxylate (5e)

White solid, mp: 209–210 °C.

IR (KBr, ν, cm^{-1}): 2957, 1703, 1626, 1557, 1490, 1456, 1397, 1375, 1287, 1218, 1041, 1014, 822, 756, 689. ^1H NMR (400 MHz, DMSO-d_6) δ: 9.99 (s, 1H, OH), 7.60 (d, J=7.6 Hz, 1H, Ar–H), 7.55 (d, J=8.0 Hz, 2H, Ar–H), 7.49 (t, J=7.6 Hz, 2H, Ar–H), 7.44–7.37 (m, 2H, Ar–H), 7.31–7.08 (m, 6H, Ar–H), 6.66 (s, 1H, Ar–H), 6.44 (d, J=7.2 Hz, 1H), Ar–H, 4.56 (s, 1H, CH), 4.24–4.01 (m, 2H, CH_2), 2.83 (d, J=16.0 Hz, 1H, CH_2), 2.06 (d, J=16.4 Hz, 1H, CH_2), 1.28 (t, J=7.0 Hz, 3H, CH_3), 1.22 (s, 3H, CH_3), 0.86 (s, 3H, CH_3). HRMS (ESI) m/z: calcd for $C_{34}H_{30}BrN_3O_4$: 623.1243; found: 623.1265.

4.8. Ethyl 4-(1-(4-bromophenyl)-2-(4-chlorophenyl)-4,5,6,7-tetrahydro-6,6-dimethyl-4-oxo-1*H*-indol-7-yl)-5-hydroxy-1-phenyl-1*H*-pyrazole-3-carboxylate (5f)

White solid, mp: 245–246 °C.

IR (KBr, ν, cm^{-1}): 2958, 1716, 1704, 1622, 1575, 1491, 1469, 1417, 1216, 1094, 1042, 1014, 831, 803, 757, 695, 640. ^1H NMR (400 MHz, $CDCl_3$) δ: 7.69 (d, J=8.0 Hz, 2H, Ar–H), 7.52 (d, J=6.4 Hz, 1H, Ar–H),

7.44 (t, J=7.6 Hz, 2H, Ar–H), 7.40–7.28 (m, 2H, Ar–H), 7.15–7.02 (m, 3H, Ar–H), 6.90 (d, J=8.4 Hz, 2H, Ar–H), 6.59–6.47 (m, 2H, Ar–H), 4.68 (s, 1H, CH), 4.40–4.20 (m, 2H, CH_2), 2.87 (d, J=17.2 Hz, 1H, CH_2), 2.36–2.19 (m, 1H, CH_2), 1.37 (t, J=7.2 Hz, 3H, CH_3), 1.26 (s, 3H, CH_3), 0.98 (s, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$) (δ, ppm): 197.6, 162.6, 149.4, 148.6, 140.0, 137.7, 136.1, 136.0, 133.3, 132.1, 129.6, 129.3, 129.0, 128.6, 127.9, 123.9, 122.9, 119.7, 105.9, 105.7, 61.0, 48.8, 38.8, 38.2, 28.8, 27.3, 14.4. HRMS (ESI) m/z: calcd for $C_{34}H_{29}BrClN_3O_4$: 657.0850 $[M-H]^-$; found: 657.0854.

4.9. Ethyl 4-(1,2-bis(4-bromophenyl)-6,6-dimethyl-4-oxo-4,5,6,7-tetrahydro-1*H*-indol-7-yl)-5-hydroxy-1-phenyl-1*H*-pyrazole-3-carboxylate (5g)

White solid, mp: 235–237 °C.

IR (KBr, ν, cm^{-1}): 2957, 1716, 1703, 1622, 1594, 1490, 1469, 1402, 1217, 1174, 1043, 1010, 828, 802, 753, 695. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.70 (d, J=7.6 Hz, 2H, Ar–H), 7.51 (d, J=7.6 Hz, 1H, Ar–H), 7.44 (t, J=7.6 Hz, 2H, Ar–H), 7.35 (t, J=7.2 Hz, 1H, Ar–H), 7.31–7.22 (m, 3H, Ar–H), 7.06 (d, J=7.6 Hz, 1H, Ar–H), 6.78 (d, J=8.4 Hz, 2H, Ar–H), 6.57 (d, J=8.0 Hz, 1H, Ar–H), 6.37 (s, 1H, Ar–H), 4.66 (s, 1H, CH), 4.38–4.18 (m, 2H, CH_2), 2.89 (d, J=17.6 Hz, 1H, CH_2), 2.09 (d, J=17.2 Hz, 1H, CH_2), 1.37 (t, J=7.2 Hz, 3H, CH_3), 1.22 (s, 3H, CH_3), 0.94 (s, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$) (δ, ppm): 197.4, 162.9, 159.6, 149.5, 148.9, 139.9, 137.8, 136.2, 132.9, 130.1, 129.6, 129.3, 128.9, 128.8, 128.3, 127.8, 123.9, 119.3, 114.6, 113.8, 106.2, 105.2, 55.4, 51.5, 48.9, 38.6, 38.2, 28.8, 27.3, 14.3. HRMS (ESI) m/z: calcd for $C_{34}H_{29}Br_2N_3O_4$: 702.0424 $[M-H]^-$; found: 702.0424.

4.10. Methyl 4-(1-(4-fluorophenyl)-4,5,6,7-tetrahydro-6,6-dimethyl-4-oxo-2-phenyl-1*H*-indol-7-yl)-5-hydroxy-1-phenyl-1*H*-pyrazole-3-carboxylate (5h)

White solid, mp: 230–231 °C.

IR (KBr, ν, cm^{-1}): 2956, 1716, 1622, 1598, 1540, 1472, 1398, 1217, 1173, 1093, 1044, 806, 753, 695. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.68 (d, J=7.2 Hz, 2H, Ar–H), 7.43 (t, J=7.2 Hz, 2H, Ar–H), 7.34 (t, J=7.2 Hz, 2H, Ar–H), 7.26 (s, 1H, Ar–H), 7.16–6.97 (m, 6H, Ar–H), 6.80 (s, 1H, Ar–H), 6.67–6.50 (m, 2H, Ar–H), 4.69 (s, 1H, CH), 3.80 (s, 3H, CH_3), 2.86 (d, J=17.2 Hz, 1H, CH_2), 2.23 (d, J=17.6 Hz, 1H, CH_2), 1.30 (s, 3H, CH_3), 1.00 (s, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$) (δ, ppm): 197.7, 163.0, 162.2 ($^1J_{CF}$=249.4 Hz), 149.6, 148.5, 139.7, 137.8, 137.4, 133.3 ($^4J_{CF}$=3.2 Hz), 131.3, 129.6 ($^3J_{CF}$=7.6 Hz), 129.0, 128.3, 128.1, 127.8, 127.2, 123.9, 119.5, 115.9 ($^2J_{CF}$=23.6 Hz), 106.3, 105.3, 51.7, 48.9, 38.6, 38.1, 28.9, 27.3. HRMS (ESI) m/z: calcd for $C_{33}H_{28}FN_3O_4$: 548.1986 $[M-H]^-$; found: 548.2000.

4.11. Methyl 4-(2-(4-chlorophenyl)-1-(4-fluorophenyl)-4,5,6,7-tetrahydro-6,6-dimethyl-4-oxo-1*H*-indol-7-yl)-5-hydroxy-1-phenyl-1*H*-pyrazole-3-carboxylate (5i)

White solid, mp: 240–241 °C.

IR (KBr, ν, cm^{-1}): 2959, 2929, 2873, 1740, 1713, 1650, 1531, 1384, 1353, 1234, 1204, 1164, 1099, 1046, 730, 688, 613, 555. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.69 (d, J=7.6 Hz, 2H, Ar–H), 7.44 (t, J=7.6 Hz, 2H, Ar–H), 7.35 (t, J=7.2 Hz, 1H, Ar–H), 7.20 (s, 1H, Ar–H), 7.10 (d, J=8.4 Hz, 3H, Ar–H), 6.89 (d, J=8.4 Hz, 2H, Ar–H), 6.83 (s, 1H, Ar–H), 6.59 (s, 1H, Ar–H), 6.52 (s, 1H, Ar–H), 6.52 (s, 1H, Ar–H), 4.67 (s, 1H, CH), 3.80 (s, 3H, CH_3), 2.87 (d, J=17.2 Hz, 1H, CH_2), 2.25–2.17 (m, 1H, CH_2), 1.27 (s, 3H, CH_3), 0.98 (s, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$) (δ, ppm): 163.0, 162.3 ($^1J_{CF}$=250.0 Hz), 149.5, 139.7, 137.7, 136.2, 133.2 ($^4J_{CF}$=3.6 Hz), 133.0, 129.7 ($^3J_{CF}$=8.8 Hz), 129.4, 129.0, 128.5, 127.9, 123.8, 119.5, 116.1 ($^2J_{CF}$=23.6 Hz), 105.5, 51.7, 48.8, 38.6, 38.1, 28.9, 27.3. HRMS (ESI) m/z: calcd for $C_{33}H_{27}ClFN_3O_4$: 582.1596 $[M-H]^-$; found: 582.1595.

4.12. Methyl 4-(2-(4-bromophenyl)-1-(4-fluorophenyl)-4,5,6,7-tetrahydro-6,6-dimethyl-4-oxo-1*H*-indol-7-yl)-5-hydroxy-1-phenyl-1*H*-pyrazole-3-carboxylate (5j)

White solid, mp: 245–246 °C.

IR (KBr, ν, cm^{-1}): 2956, 1721, 1710, 1622, 1511, 1471, 1415, 1284, 1219, 1197, 1170, 1043, 853, 809, 748, 650. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.30 (s, 1H, OH), 7.69 (d, J=7.6 Hz, 2H, Ar–H), 7.44 (t, J=7.6 Hz, 2H, Ar–H), 7.35 (t, J=7.2 Hz, 1H, Ar–H), 7.28–7.16 (m, 3H, Ar–H), 7.08 (s, 1H, Ar–H), 6.82 (d, J=8.4 Hz, 3H, Ar–H), 6.61 (s, 1H, Ar–H), 6.48 (s, 1H, Ar–H), 4.66 (s, 1H, CH), 3.79 (s, 3H, CH_3), 2.88 (d, J=17.2 Hz, 1H, CH_2), 2.16 (d, J=17.2 Hz, 1H, CH_2), 1.26 (s, 3H, CH_3), 0.97 (s, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$) (δ, ppm): 197.7, 163.0, 162.3 ($^1J_{CF}$=250.0 Hz), 149.5, 148.9, 139.7, 137.7, 136.2, 133.0 ($^4J_{CF}$=3.2 Hz), 131.5, 130.1 ($^3J_{CF}$=9.4 Hz), 129.6, 129.0, 127.9, 123.9, 121.4, 119.5, 116.1 (d, J=22.4 Hz, 1H), 106.2, 105.5, 51.7, 48.8, 38.6, 38.1, 28.9, 27.3. HRMS (ESI) m/z: calcd for $C_{33}H_{27}BrFN_3O_4$: 628.1071 $[M-H]^-$; found: 628.1069.

4.13. Methyl 4-(1-(4-fluorophenyl)-4,5,6,7-tetrahydro-6,6-dimethyl-4-oxo-2-*p*-tolyl-1*H*-indol-7-yl)-5-hydroxy-1-phenyl-1*H*-pyrazole-3-carboxylate (5k)

White solid, mp: 228–229 °C.

IR (KBr, ν, cm^{-1}): 2956, 1716, 1624, 1598, 1596, 1510, 1446, 1379, 1219, 1179, 1170, 1043, 853, 819, 798, 753, 695. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.67 (d, J=7.2 Hz, 2H, Ar–H), 7.43 (t, J=7.2 Hz, 2H, Ar–H), 7.34 (t, J=7.2 Hz, 1H, Ar–H), 7.25–7.04 (m, 2H, Ar–H), 6.97–6.89 (m, 4H, Ar–H), 6.78 (s, 1H, Ar–H), 6.70–6.48 (m, 2H, Ar–H), 4.68 (s, 1H, CH), 3.80 (s, 3H, CH_3), 2.83 (d, J=15.6 Hz, 1H, CH_2), 2.37–2.23 (m, 4H, CH_2, CH_3), 1.30 (s, 3H, CH_3), 1.00 (s, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$) (δ, ppm): 163.0, 162.2 ($^1J_{CF}$=249.6 Hz), 149.6, 139.7, 137.7, 137.6, 137.0, 133.3 ($^4J_{CF}$=3.2 Hz), 129.0, 128.9 ($^3J_{CF}$=9.6 Hz), 128.9, 128.4, 128.2, 127.8, 123.7, 123.7, 119.5, 116.1 ($^2J_{CF}$=22.4 Hz), 113.2, 104.8, 51.7, 48.9, 38.7, 38.2, 28.9, 27.3, 21.2. HRMS (ESI) m/z: calcd for $C_{34}H_{30}FN_3O_4$: 562.2142 $[M-H]^-$; found: 562.2130.

4.14. Ethyl 4-(2-(4-bromophenyl)-1-(4-fluorophenyl)-6,6-dimethyl-4-oxo-4,5,6,7-tetrahydro-1*H*-indol-7-yl)-5-hydroxy-1-phenyl-1*H*-pyrazole-3-carboxylate (5l)

White solid, mp: 229–231 °C.

IR (KBr, ν, cm^{-1}): 2958, 1715, 1704, 1621, 1595, 1510, 1469, 1402, 1283, 1217, 1190, 1174, 1043, 1009, 853, 824, 797, 747. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 10.14 (s, 1H, OH), 7.71 (d, J=7.6 Hz, 2H, Ar–H), 7.43 (t, J=7.2 Hz, 2H, Ar–H), 7.34 (t, J=7.2 Hz, 1H, Ar–H), 7.23 (d, J=8.0 Hz, 2H, Ar–H), 7.17 (s, 1H, Ar–H), 7.07 (t, J=7.6 Hz, 1H, Ar–H), 6.85 (t, J=7.6 Hz, 1H, Ar–H), 6.78 (d, J=7.6 Hz, 2H, Ar–H), 6.68 (s, 1H, Ar–H), 6.37 (s, 1H, Ar–H), 4.65 (s, 1H, CH), 4.37–4.15 (m, 2H, CH_2), 2.89 (d, J=17.6 Hz, 1H, CH_2), 2.08 (d, J=17.2 Hz, 1H, CH_2), 1.34 (t, J=7.0 Hz, 3H, CH_3), 1.23 (s, 3H, CH_3), 0.94 (s, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$) (δ, ppm): 196.9, 162.28 ($^1J_{CF}$=249.8 Hz), 148.3, 140.0, 137.7, 136.3, 132.9 ($^4J_{CF}$=3.2 Hz), 130.1, 129.9 ($^3J_{CF}$=9.6 Hz), 129.6, 123.0, 127.9, 123.7, 121.5, 119.6, 116.1 ($^2J_{CF}$=24.4 Hz), 105.6, 60.8, 48.9, 38.8, 38.2, 28.7, 27.2, 14.3. HRMS (ESI) m/z: calcd for $C_{34}H_{29}BrFN_3O_4$: 642.1227 $[M-H]^-$; found: 642.1227.

4.15. Methyl 4-(1-(4-chlorophenyl)-4,5,6,7-tetrahydro-6,6-dimethyl-4-oxo-2-phenyl-1*H*-indol-7-yl)-5-hydroxy-1-phenyl-1*H*-pyrazole-3-carboxylate (5m)

White solid, mp: 262–263 °C.

IR (KBr, ν, cm^{-1}): 2956, 1717, 1707, 1624, 1598, 1560, 1495, 1468, 1441, 1376, 1284, 1217, 1711, 1043, 841, 810, 758, 696. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.50 (s, 1H, OH), 7.68 (d, J=7.1 Hz, 2H, Ar–H), 7.48–7.31 (m, 4H, Ar–H), 7.23–6.99 (m, 7H, Ar–H), 6.64–6.46 (m, 2H, Ar–H), 4.68 (s, 1H, CH), 3.82 (s, 3H, CH_3), 2.87 (d, J=16.9 Hz, 1H,

CH_2), 2.22 (d, J=17.7 Hz, 1H, CH_2), 1.29 (s, 3H, CH_3), 0.99 (s, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$) (δ, ppm): 197.7, 163.0, 149.6, 148.4, 139.7, 137.7, 137.3, 135.8, 134.6, 131.2, 129.0, 128.3, 128.2, 127.9, 127.2, 123.9, 119.6, 106.3, 105.3, 51.8, 48.9, 38.5, 38.1, 29.0, 27.3. HRMS (ESI) m/z: calcd for $C_{33}H_{28}ClN_3O_4$: 564.1690 $[M-H]^-$; found: 564.1689.

4.16. Methyl 4-(1,2-bis(4-chlorophenyl)-4,5,6,7-tetrahydro-6,6-dimethyl-4-oxo-1*H*-indol-7-yl)-5-hydroxy-1-phenyl-1*H*-pyrazole-3-carboxylate (5n)

White solid, mp: 265–267 °C.

IR (KBr, ν, cm^{-1}): 2956, 1720, 1709, 1622, 1597, 1548, 1470, 1398, 1217, 1197, 1172, 1092, 1043, 831, 800, 753, 695, 642. ^1H NMR (400 MHz, $CDCl_3$) δ: 7.67 (d, J=8.0 Hz, 2H, Ar–H), 7.48–7.33 (m, 4H, Ar–H), 7.22–7.06 (m, 4H, Ar–H), 6.91 (d, J=8.4 Hz, 2H, Ar–H), 6.56 (s, 2H, Ar–H), 4.67 (s, 1H, CH), 3.82 (s, 3H, CH_3), 2.89 (d, J=17.2 Hz, 1H, CH_2), 2.14–2.08 (m, 1H, CH_2), 1.28 (s, 3H, CH_3), 0.99 (s, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$) (δ, ppm): 197.9, 163.0, 149.5, 148.8, 139.7, 137.7, 136.0, 135.5, 134.9, 133.2, 129.6, 129.4, 129.2, 129.0, 128.5, 128.0, 123.9, 119.6, 106.4, 105.6, 51.8, 48.8, 38.5, 38.1, 28.9, 27.3. HRMS (ESI) m/z: calcd for $C_{33}H_{27}Cl_2N_3O_4$: 598.1300 $[M-H]^-$; found: 598.1300.

4.17. Methyl 4-(2-(4-bromophenyl)-1-(4-chlorophenyl)-4,5,6,7-tetrahydro-6,6-dimethyl-4-oxo-1*H*-indol-7-yl)-5-hydroxy-1-phenyl-1*H*-pyrazole-3-carboxylate (5o)

White solid, mp: 267–268 °C.

IR (KBr, ν, cm^{-1}): 2955, 1720, 1708, 1621, 1596, 1545, 1494, 1468, 1378, 1217, 1711, 1042, 1010, 827, 808, 799, 730. ^1H NMR (400 MHz, $CDCl_3$) δ: 7.68 (d, J=8.0 Hz, 2H, Ar–H), 7.43 (t, J=7.6 Hz, 2H, Ar–H), 7.35 (t, J=7.2 Hz, 1H, Ar–H), 7.26–7.17 (m, 3H, Ar–H), 7.08 (s, 1H, Ar–H), 6.83 (d, J=8.0 Hz, 3H, Ar–H), 6.61 (s, 1H, Ar–H), 6.49 (s, 1H, Ar–H), 4.66 (s, 1H, CH), 3.79 (s, 3H, CH_3), 2.89 (d, J=17.2 Hz, 1H, CH_2), 2.15 (d, J=16.8 Hz, 1H, CH_2), 1.26 (s, 3H, CH_3), 0.97 (s, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$) (δ, ppm): 197.9, 163.0, 149.5, 148.9, 139.7, 137.7, 136.0, 135.5, 134.9, 131.5, 130.1, 129.6, 129.2, 129.0, 128.0, 123.9, 121.5, 119.6, 106.4, 105.6, 51.8, 48.8, 38.5, 38.1, 28.9, 27.3. HRMS (ESI) m/z: calcd for $C_{33}H_{27}BrClN_3O_4$: 644.0712 $[M-H]^-$; found: 644.0727.

4.18. Methyl 4-(1-(4-chlorophenyl)-4,5,6,7-tetrahydro-6,6-dimethyl-4-oxo-2-*p*-tolyl-1*H*-indol-7-yl)-5-hydroxy-1-phenyl-1*H*-pyrazole-3-carboxylate (5p)

White solid, mp: 255–257 °C.

IR (KBr, ν, cm^{-1}): 2957, 1716, 1708, 1631, 1594, 1495, 1446, 1402, 1285, 1218, 1198, 1172, 1090, 1043, 1019, 824, 800, 727, 684. ^1H NMR (400 MHz, $CDCl_3$) δ: 8.36 (s, 1H, OH), 7.68 (d, J=7.6 Hz, 2H, Ar–H), 7.43 (t, J=7.3 Hz, 2H, Ar–H), 7.40–7.29 (m, 2H, Ar–H), 7.21–7.05 (m, 2H, Ar–H), 6.98–6.85 (m, 4H, Ar–H), 6.69–6.35 (m, 2H, Ar–H), 4.66 (s, 1H, CH), 3.81 (s, 3H, CH_3), 2.85 (d, J=17.1 Hz, 1H, CH_2), 2.30–2.18 (m, 4H, CH_3, CH_2), 1.29 (s, 3H, CH_3), 0.99 (s, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$) (δ): 197.5, 163.0, 149.6, 148.1, 139.7, 137.7, 137.4, 137.0, 135.9, 134.5, 129.0, 128.9, 128.3, 128.3, 127.8, 123.8, 119.5, 106.2, 104.9, 51.8, 48.8, 38.6, 38.1, 28.9, 27.3, 21.2. HRMS (ESI) m/z: calcd for $C_{34}H_{30}ClN_3O_4$: 578.1847 $[M-H]^-$; found: 578.1847.

4.19. Ethyl 4-(1,2-bis(4-chlorophenyl)-4,5,6,7-tetrahydro-6,6-dimethyl-4-oxo-1*H*-indol-7-yl)-5-hydroxy-1-phenyl-1*H*-pyrazole-3-carboxylate (5q)

White solid, mp: 242 °C.

IR (KBr, ν, cm^{-1}): 2958, 1716, 1704, 1647, 1622, 1576, 1542, 1495, 1458, 1396, 1217, 1176, 1092, 1043, 959, 908. ^1H NMR (400 MHz, $CDCl_3$) δ: 7.68 (d, J=7.6 Hz, 2H, Ar–H), 7.44 (t, J=7.6 Hz, 2H, Ar–H), 7.41–7.32 (m, 2H, Ar–H), 7.22–7.08 (m, 4H, Ar–H), 6.91 (d, J=7.6 Hz, 2H, Ar–H), 6.57 (s, 2H, Ar–H), 4.68 (s, 1H, CH), 4.38–4.20 (m, 2H, CH_2), 2.86 (d, J=17.2 Hz, 1H, CH_2), 2.36–2.22 (m, 1H, CH_2), 1.36 (t, J=7.2 Hz, 3H, CH_3), 1.26 (s, 3H, CH_3), 0.99 (s, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$) (δ, ppm): 162.6, 149.3, 140.0, 137.7, 136.2, 135.5, 134.9, 133.3, 129.6, 129.5, 129.3, 129.1, 129.0, 128.6, 127.9, 123.8, 119.7, 105.7, 60.9, 48.9, 38.8, 38.2, 28.7, 27.2, 14.4. HRMS (ESI) m/z: calcd for $C_{34}H_{29}Cl_2N_3O_4$: 612.1457 $[M-H]^-$; found: 612.1460.

4.20. Ethyl 4-(2-(4-bromophenyl)-1-(4-chlorophenyl)-6,6-dimethyl-4-oxo-4,5,6,7-tetrahydro-1*H*-indol-7-yl)-5-hydroxy-1-phenyl-1*H*-pyrazole-3-carboxylate (5r)

White solid, mp: 231–233 °C.

IR (KBr, ν, cm^{-1}): 2958, 1716, 1703, 1622, 1594, 1402, 1282, 1217, 1172, 1091, 1043, 1009, 827, 801, 756, 730. ^1H NMR (400 MHz, $CDCl_3$) δ: 9.87 (s, 1H, OH), 7.71 (d, J=7.6 Hz, 2H, Ar–H), 7.44 (t, J=7.6 Hz, 2H, Ar–H), 7.40–7.31 (m, 2H, Ar–H), 7.25 (d, J=8.4 Hz, 2H, Ar–H), 7.13 (s, 2H, Ar–H), 6.78 (d, J=8.0 Hz, 2H, Ar–H), 6.62 (d, J=6.8 Hz, 1H, Ar–H), 6.39 (s, 1H, Ar–H), 4.66 (s, 1H, CH), 4.42–4.18 (m, 2H, CH_2), 2.89 (d, J=17.2 Hz, 1H, CH_2), 2.11 (d, J=17.2 Hz, 1H, CH_2), 1.36 (t, J=6.8 Hz, 3H, CH_3), 1.23 (s, 3H, CH_3), 0.95 (s, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$) (δ, ppm): 197.4, 162.6, 149.4, 148.5, 140.0, 137.7, 136.1, 135.5, 134.9, 131.5, 130.0, 129.6, 129.0, 127.9, 123.9, 121.5, 119.7, 105.7, 60.9, 48.9, 38.8, 38.2, 28.8, 27.2, 14.4. HRMS (ESI) m/z: calcd for $C_{34}H_{29}BrClN_3O_4$: 658.0928 $[M-H]^-$; found: 658.0929.

4.21. Methyl 4-(4,5,6,7-tetrahydro-6,6-dimethyl-4-oxo-2-phenyl-1-*p*-tolyl-1*H*-indol-7-yl)-5-hydroxy-1-phenyl-1*H*-pyrazole-3-carboxylate (5s)

White solid, mp: 251–253 °C.

IR (KBr, ν, cm^{-1}): 2957, 1709, 1625, 1503, 1435, 1402, 1237, 1198, 1151, 1044, 1018, 847, 807, 772, 750, 699. ^1H NMR (400 MHz, DMSO-d_6) δ: 10.01 (s, 1H, OH), 7.56 (d, J=7.6 Hz, 2H, Ar–H), 7.48 (t, J=7.6 Hz, 2H, Ar–H), 7.38 (t, J=7.6 Hz, 1H, Ar–H), 7.26–7.08 (m, 7H, Ar–H), 6.82 (d, J=6.0 Hz, 1H, Ar–H), 6.65 (s, 1H, Ar–H), 6.33 (d, J=7.6 Hz, 1H, Ar–H), 4.50 (s, 1H, CH), 3.65 (s, 3H, CH_3), 2.86 (d, J=16.8 Hz, 1H, CH_2), 2.26 (s, 3H, CH_3), 2.15–2.10 (m, 1H, CH_2), 1.22 (s, 3H, CH_3), 0.86 (s, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$) (δ, ppm): 162.9, 149.5, 139.8, 138.6, 137.7, 137.6, 134.6, 131.5, 128.9, 128.2, 128.1, 127.8, 127.0, 123.8, 119.3, 105.1, 51.5, 49.1, 38.8, 38.2, 28.8, 27.3, 21.2. HRMS (ESI) m/z: calcd for $C_{34}H_{31}N_3O_4$: 544.2236 $[M-H]^-$; found: 544.2239.

4.22. Methyl 4-(2-(4-chlorophenyl)-4,5,6,7-tetrahydro-6,6-dimethyl-4-oxo-1-*p*-tolyl-1*H*-indol-7-yl)-5-hydroxy-1-phenyl-1*H*-pyrazole-3-carboxylate (5t)

White solid, mp: 256–258 °C.

IR (KBr, ν, cm^{-1}): 2957, 1719, 1711, 1622, 1597, 1543, 1515, 1458, 1397, 1216, 1172, 1120, 1043, 831, 808, 752, 695. ^1H NMR (400 MHz, $CDCl_3$) δ: 7.69 (d, J=7.6 Hz, 2H, Ar–H), 7.43 (t, J=7.6 Hz, 2H, Ar–H), 7.34 (t, J=7.2 Hz, 1H, Ar–H), 7.17 (s, 1H, Ar–H), 7.07 (d, J=8.4 Hz, 3H, Ar–H), 6.91 (d, J=8.4 Hz, 3H, Ar–H), 6.50 (s, 2H, Ar–H), 4.64 (s, 1H, CH), 3.76 (s, 3H, CH_3), 2.88 (d, J=17.6 Hz, 1H, CH_2), 2.33 (s, 3H, CH_3), 2.20–2.13 (m, 1H, CH_2), 1.26 (s, 3H, CH_3), 0.97 (s, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$) (δ, ppm): 197.5, 162.9, 149.5, 148.9, 139.8, 138.8, 137.8, 136.1, 134.4, 132.9, 130.1, 129.8, 129.5, 129.3, 128.9, 128.3, 128.0, 127.8, 127.5, 123.9, 119.4, 106.4, 105.3, 51.5, 48.9, 38.5, 38.2, 28.9, 27.3, 21.2. HRMS (ESI) m/z: calcd for $C_{34}H_{30}ClN_3O_4$: 578.1847 $[M-H]^-$; found: 578.1846.

4.23. Methyl 4-(2-(4-bromophenyl)-4,5,6,7-tetrahydro-6,6-dimethyl-4-oxo-1-*p*-tolyl-1*H*-indol-7-yl)-5-hydroxy-1-phenyl-1*H*-pyrazole-3-carboxylate (5u)

White solid, mp: 248–249 °C.

IR (KBr, ν, cm^{-1}): 2956, 1719, 1711, 1596, 1543, 1459, 1418, 1378, 1283, 1216, 1172, 1092, 1043, 1008, 959, 799, 754. ^1H NMR (400 MHz,

$CDCl_3$) δ: 7.68 (d, J=8.0 Hz, 2H, Ar–H), 7.49–7.40 (m, 2H, Ar–H), 7.35 (t, J=7.2 Hz, 1H, Ar–H), 7.25–7.07 (m, 4H, Ar–H), 6.92 (d, J=7.2 Hz, 1H, Ar–H), 6.87 (d, J=8.4 Hz, 2H, Ar–H), 6.55 (s, 1H, Ar–H), 6.45 (d, J=7.2 Hz, 1H, Ar–H), 4.65 (s, 1H, CH), 3.77 (s, 3H, CH_3), 2.86 (d, J=16.8 Hz, 1H, CH_2), 2.33 (s, 3H, CH_3), 2.19 (d, J=17.6 Hz, 1H, CH_2), 1.27 (s, 3H, CH_3), 0.98 (s, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$) (δ, ppm): 197.5, 162.9, 149.5, 148.8, 139.8, 138.8, 137.8, 136.1, 134.4, 131.3, 130.5, 129.8, 129.6, 128.9, 128.0, 127.8, 127.5, 123.9, 121.1, 119.4, 106.2, 105.4, 51.5, 48.9, 38.6, 38.2, 28.8, 27.3, 21.2. HRMS (ESI) m/z: calcd for $C_{34}H_{30}BrN_3O_4$: 624.1322 $[M-H]^-$; found: 622.1324.

4.24. Methyl 4-(4,5,6,7-tetrahydro-6,6-dimethyl-4-oxo-1,2-di*p*-tolyl-1*H*-indol-7-yl)-5-hydroxy-1-phenyl-1*H*-pyrazole-3-carboxylate (5v)

White solid, mp: 228–229 °C.

IR (KBr, ν, cm^{-1}): 2956, 1715, 1623, 1597, 1558, 1515, 1458, 1471, 1377, 1284, 1216, 1171, 1043, 823, 800, 754. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.68 (d, J=7.7 Hz, 2H, Ar–H), 7.49–7.38 (m, 2H, Ar–H), 7.33 (t, J=7.2 Hz, 1H, Ar–H), 7.14 (d, J=11.2 Hz, 2H, Ar–H), 6.96–6.86 (m, 5H, Ar–H), 6.56 (s, 1H, Ar–H), 6.46 (s, 1H, Ar–H), 4.64 (s, 1H, CH), 3.76 (s, 3H, CH_3), 2.87 (d, J=17.2 Hz, 1H, CH_2), 2.32 (s, 3H, CH_3), 2.27–2.14 (m, 4H, CH_3, CH_2), 1.28 (s, 3H, CH_3), 0.98 (s, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$) (δ, ppm): 197.2, 162.9, 149.6, 148.1, 139.8, 138.4, 137.8, 137.5, 136.6, 134.8, 129.6, 129.4, 128.0, 128.8, 128.1, 127.7, 127.5, 123.9, 119.3, 106.1, 104.7, 77.4, 77.1, 76.8, 51.5, 49.0, 38.6, 38.2, 28.9, 27.3, 21.2. HRMS (ESI) m/z: calcd for $C_{35}H_{33}N_3O_4$: 558.2393 $[M-H]^-$; found: 558.2395.

4.25. Ethyl 4-(2-(4-chlorophenyl)-4,5,6,7-tetrahydro-6,6-dimethyl-4-oxo-1-*p*-tolyl-1*H*-indol-7-yl)-5-hydroxy-1-phenyl-1*H*-pyrazole-3-carboxylate (5w)

White solid, mp: 219 °C.

IR (KBr, ν, cm^{-1}): 2964, 1707, 1619, 1595, 1514, 1493, 1458, 1416, 1313, 1263, 1166, 1155, 1039, 1014, 866, 758, 696. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.68 (d, J=8.0 Hz, 2H, Ar–H), 7.43 (t, J=7.6 Hz, 2H, Ar–H), 7.34 (t, J=7.2 Hz, 1H, Ar–H), 7.21–7.05 (m, 4H, Ar–H), 7.01–6.87 (m, 3H, Ar–H), 6.63 (s, 1H, Ar–H), 6.47 (s, 1H, Ar–H), 4.66 (s, 1H, CH), 4.33–4.15 (m, 2H, CH_2), 2.84 (d, J=17.2 Hz, 1H, CH_2), 2.32 (s, 3H, CH_3), 2.28–2.21 (m, 1H, CH_2), 1.32 (t, J=7.2 Hz, 3H, CH_3), 1.27 (s, 3H, CH_3), 0.99 (s, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$) (δ, ppm): 197.2, 162.5, 149.4, 148.6, 140.1, 138.8, 137.8, 136.2, 134.4, 132.9, 130.0, 129.9, 129.6, 129.3, 128.9, 128.4, 127.9, 127.8, 127.5, 123.9, 119.4, 105.4, 60.6, 48.9, 38.8, 38.3, 28.7, 27.3, 21.2, 14.3. HRMS (ESI) m/z: calcd for $C_{35}H_{32}ClN_3O_4$: 592.2003 $[M-H]^-$; found: 592.2021.

4.26. Methyl 4-(4,5,6,7-tetrahydro-1-(4-methoxyphenyl)-6,6-dimethyl-4-oxo-2-phenyl-1*H*-indol-7-yl)-5-hydroxy-1-phenyl-1*H*-pyrazole-3-carboxylate (5x)

White solid, mp: 255–257 °C.

IR (KBr, ν, cm^{-1}): 2958, 1716, 1620, 1598, 1512, 1471, 1442, 1381, 1246, 1216, 1171, 1035, 841, 809, 759, 652. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.69 (d, J=7.8 Hz, 2H, Ar–H), 7.43 (t, J=7.2 Hz, 2H, Ar–H), 7.33 (t, J=7.2 Hz, 1H, Ar–H), 7.19–6.99 (m, 6H, Ar–H), 6.88 (s, 1H, Ar–H), 6.67–6.58 (m, 1H, Ar–H), 6.50 (s, 1H, Ar–H), 4.66 (s, 1H, CH), 3.77 (s, 6H, CH_3), 2.88 (d, J=17.2 Hz, 1H, CH_2), 2.22 (d, J=17.6 Hz, 1H, CH_2), 1.29 (s, 3H, CH_3), 1.00 (s, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$) (δ, ppm): 197.2, 163.0, 159.4, 149.6, 148.5, 139.9, 137.8, 137.5, 131.6, 129.9, 129.4, 128.9, 128.2, 128.1, 127.8, 126.9, 123.8, 119.3, 114.4, 113.8, 106.0, 105.0, 55.4, 51.5, 49.0, 38.6, 38.22, 28.9, 27.3. HRMS (ESI) m/z: calcd for $C_{34}H_{31}N_3O_5$: 560.2185 $[M-H]^-$; found: 560.2184.

4.27. Methyl 4-(2-(4-chlorophenyl)-1-(4-methoxyphenyl)-6,6-dimethyl-4-oxo-4,5,6,7-tetrahydro-1*H*-indol-7-yl)-5-hydroxy-1-phenyl-1*H*-pyrazole-3-carboxylate (5y)

White solid, mp: 272–274 °C.

IR (KBr, ν, cm^{-1}): 2966, 1704, 1617, 1514, 1493, 1458, 1416, 1313, 1263, 1155, 1040, 1014, 759, 696. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.72 (d, J=8.0 Hz, 2H, Ar–H), 7.44 (t, J=7.6 Hz, 2H, Ar–H), 7.35 (t, J=7.2 Hz, 1H, Ar–H), 7.14–7.01 (m, 3H, Ar–H), 6.88 (d, J=8.0 Hz, 3H, Ar–H), 6.64 (d, J=8.4 Hz, 1H, Ar–H), 6.56 (d, J=8.4 Hz, 1H, Ar–H), 6.40 (s, 1H, Ar–H), 4.63 (s, 1H, CH), 3.79 (s, 3H, CH_2), 3.76 (s, 3H, CH_2), 2.92 (d, J=17.6 Hz, 1H, CH_2), 2.13 (d, J=17.2 Hz, 1H, CH_2), 1.25 (s, 3H, CH_3), 0.96 (s, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$) (δ, ppm): 197.4, 162.9, 159.6, 149.5, 148.9, 137.8, 136.2, 132.9, 130.1, 129.6, 129.3, 128.9, 128.8, 128.3, 127.8, 123.7, 119.3, 114.6, 113.8, 106.2, 105.2, 55.4, 51.5, 48.9, 38.6, 38.2, 28.8, 27.3. HRMS (ESI) m/z: calcd for $C_{34}H_{30}ClN_3O_4$: 594.1796 $[M-H]^-$; found: 594.1796.

4.28. Methyl 4-(2-(4-bromophenyl)-4,5,6,7-tetrahydro-1-(4-methoxyphenyl)-6,6-dimethyl-4-oxo-1*H*-indol-7-yl)-5-hydroxy-1-phenyl-1*H*-pyrazole-3-carboxylate (5z)

White solid, mp: 268–270 °C.

IR (KBr, ν, cm^{-1}): 2956, 1719, 1711, 1596, 1543, 1459, 1418, 1378, 1283, 1216, 1172, 1092, 1043, 1008, 959, 799, 754. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.69 (d, J=8.0 Hz, 2H, Ar–H), 7.43 (t, J=7.2 Hz, 2H, Ar–H), 7.33 (t, J=7.2 Hz, 1H, Ar–H), 7.20–7.01 (m, 6H, Ar–H), 6.88 (s, 1H, Ar–H), 6.69–6.44 (m, 3H, Ar–H), 4.66 (s, 1H, CH), 3.77 (s, 6H, CH_3), 2.88 (d, J=17.2 Hz, 1H, CH_2), 2.22 (d, J=17.6 Hz, 1H, CH_2), 1.29 (s, 3H, CH_3), 1.00 (s, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$) (δ, ppm): 197.4, 162.9, 159.6, 149.5, 149.0, 139.9, 137.8, 136.2, 131.3, 130.5, 129.5, 129.3, 129.0, 128.8, 127.8, 123.9, 121.1, 119.3, 114.6, 113.9, 106.2, 105.3, 55.5, 51.6, 48.9, 38.6, 38.2, 28.8, 27.3. HRMS (ESI) m/z: calcd for $C_{34}H_{30}BrN_3O_4$: 638.1270 $[M-H]^-$; found: 638.1290.

4.29. Methyl 4-(4,5,6,7-tetrahydro-1-(4-methoxyphenyl)-6,6-dimethyl-4-oxo-2-*p*-tolyl-1*H*-indol-7-yl)-5-hydroxy-1-phenyl-1*H*-pyrazole-3-carboxylate (5aa)

White solid, mp: 245–247 °C.

IR (KBr, ν, cm^{-1}): 2957, 1712, 1622, 1598, 1596, 1513, 1463, 1383, 1248, 1217, 1170, 1042, 907, 808, 759, 654. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.69 (d, J=8.4 Hz, 2H, Ar–H), 7.43 (t, J=7.6 Hz, 2H, Ar–H), 7.33 (t, J=7.2 Hz, 1, Ar–H H), 7.14 (s, 1H, Ar–H), 6.99–6.84 (m, 5H, Ar–H), 6.64–6.52 (m, 2H, Ar–H), 6.48 (s, 1H, Ar–H), 4.64 (s, 1H, CH), 3.77 (s, 6H, CH_3), 2.85 (d, J=17.6 Hz, 1H, CH_2), 2.28–2.19 (m, 4H, CH_3, CH_2), 1.28 (s, 3H, CH_3), 0.99 (s, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$) (δ, ppm): 197.0, 163.0, 159.4, 149.6, 148.2, 139.9, 137.8, 137.7, 136.7, 130.0, 129.4, 128.9, 128.8, 128.7, 128.2, 127.7, 123.8, 119.2, 114.4, 113.7, 105.9, 104.6, 55.4, 51.5, 49.0, 38.7, 38.2, 28.9, 27.3, 21.2. HRMS (ESI) m/z: calcd for $C_{35}H_{33}N_3O_5$: 574.2342 $[M-H]^-$; found: 574.2343.

4.30. Ethyl 4-(4,5,6,7-tetrahydro-1-(4-methoxyphenyl)-6,6-dimethyl-4-oxo-2-phenyl-1*H*-indol-7-yl)-5-hydroxy-1-phenyl-1*H*-pyrazole-3-carboxylate (5ab)

White solid, mp: 213–215 °C.

IR (KBr, ν, cm^{-1}): 2959, 1714, 1703, 1621, 1599, 1512, 1470, 1440, 1384, 1247, 1215, 1171, 1041, 841, 776, 652. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.68 (d, J=8.0 Hz, 2H, Ar–H), 7.42 (t, J=7.6 Hz, 2H, Ar–H), 7.33 (t, J=6.8 Hz, 1H, Ar–H), 7.19–7.00 (m, 6H, Ar–H), 6.87 (s, 1H, Ar–H), 6.72 (s, 1H, Ar–H), 6.60 (s, 1H, Ar–H), 6.47 (s, 1H, Ar–H), 4.66 (s, 1H, CH), 4.24 (q, J=7.6 Hz, 1H, CH_2), 3.76 (s, 3H, CH_3), 2.80 (d, J=17.2 Hz, 1H, CH_2), 2.25 (d, J=17.6 Hz, 1H, CH_2), 1.31 (t, J=7.2 Hz, 3H, CH_3), 1.28 (s, 3H, CH_3), 1.01 (s, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$)

(δ, ppm): 196.5, 162.5, 159.4, 149.4, 147.9, 140.2, 137.8, 137.7, 131.5, 129.8, 128.9, 128.2, 128.1, 127.7, 127.0, 123.7, 119.3, 114.5, 113.8, 105.0, 104.9, 60.7, 55.4, 49.1, 39.0, 38.3, 28.7, 27.3, 14.3. HRMS (ESI) m/z: calcd for $C_{35}H_{33}N_3O_5$: 574.2342 $[M-H]^-$; found: 574.2342.

4.31. Ethyl 4-(4,5,6,7-tetrahydro-1-(4-methoxyphenyl)-6,6-dimethyl-4-oxo-2-*p*-tolyl-1*H*-indol-7-yl)-5-hydroxy-1-phenyl-1*H*-pyrazole-3-carboxylate (5ac)

White solid, mp: 193–195 °C.

IR (KBr, ν, cm^{-1}): 2966, 1703, 1615, 1593, 1513, 1497, 1445, 1385, 1253, 1214, 1118, 1035, 830, 807, 770, 650. ^1H NMR (400 MHz, $CDCl_3$) δ: 7.66 (d, J=5.6 Hz, 2H, Ar–H), 7.41 (d, J=7.2 Hz, 2H, Ar–H), 7.38–7.28 (m, 2H, Ar–H), 7.04–6.90 (m, 4H, Ar–H), 6.91–6.68 (m, 2H, Ar–H), 6.59 (s, 1H, Ar–H), 6.43 (s, 1H, Ar–H), 4.65 (s, 1H, CH), 4.35–4.16 (m, 2H, CH_2), 3.76 (s, 3H, CH_3), 2.79 (d, J=17.2 Hz, 1H, CH_2), 2.32–2.22 (m, 4H, CH_2, CH_3), 1.39–1.20 (m, 6H, CH_3), 1.01 (s, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$) (δ, ppm): 196.6, 162.5, 159.4, 149.5, 147.9, 140.2, 137.8, 137.8, 136.7, 129.9, 128.9, 128.8, 128.6, 128.1, 127.6, 123.7, 119.2, 114.4, 105.1, 104.6, 60.6, 55.4, 49.0, 38.9, 38.3, 28.7, 27.3, 21.1, 14.2. HRMS (ESI) m/z: calcd for $C_{36}H_{35}N_3O_5$: 588.2498 $[M-H]^-$; found: 588.2502.

4.32. The supporting experimental for proposed mechanism

1-(4-Bromophenyl)-4,5,6,7-tetrahydro-6,6-dimethyl-4-oxo-2-phenyl-1*H*-indol-7-yl acetate **C1** (1 mmol, 1.0 equiv) was introduced in a 10 mL vial, and methyl 5-hydroxy-1-phenyl-1*H*-pyrazole-3-carboxylate **E** (1.0 mmol, 1.0 equiv) and HOAc (2.0 mL) were added. The reaction vial was closed and pre-stirred for 20 s. The mixture was irradiated at 150 °C until the conversion of the starting material **C1** was complete, as shown by TLC. The reaction mixture was cooled to room temperature and diluted with cold water (50 mL). The solid product was collected by Büchner filtration and was purified by flash column chromatography (silica gel, mixtures of *n*-hexane/diethyl ether=7/1, v/v) to afford the desired pure products **5a** in 82% yield.

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Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.tet.2013.05.063.

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11. The single crystal growth was carried out in co-solvent of EtOH and DMF at room temperature. Crystal data for **5a** (CCDC-922114): $C_{33}H_{28}BrN_3O_4$, crystal dimension 0.42 × 0.20 × 0.13 mm, Triclinic, space group P-1, a=9.1630(10) Å, b=18.8682(16) Å, c=7.3157(6) Å, α=25.570(2)°, β=97.6530(10)°, γ=94.3680(10)°, V=2925.7(5) $Å^3$, M_r=610.49, Z=4, λ=0.71073 Å, μ (*Mo* $K\alpha$)=1.447 mm^{-1}, $F(000)$=1256, R_1=0.0441, wR_2=0.0547.
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