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Brønsted acid catalysed eco friendly synthesis of quaternary centred C-3 functionalized oxindole derivatives†

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A facile atom economic and eco friendly protocol for the synthesis of biologically important quaternary centered C-3 functionalized oxindole derivatives, with a novel nucleus, in high yields has been demonstrated by employing 3-hydroxy-2-oxindole, isoxazolone/pyrazolone and environmentally benevolent *p*-toluene sulphonic acid as a catalyst. The advantages of this protocol are the wide substrate scope, practical simplicity, benign solvent and good yields. All the synthesized compounds were evaluated for their *in vitro* anti-microbial activity. Several compounds exhibited good activities comparable to those of established standard drugs. Furthermore, the anti-cancer activity of compounds **3g** and **3m** has been preliminarly demonstrated by *in vitro* evaluation against human tumor cell lines MCF-7 and Hep-2, using MTT-based assays with commercially available standard drug cisplatin as a positive control. Gratifyingly, compounds **3g** and **3m** exhibited good *in vitro* inhibitory activities against Hep-2 and MCF-7 cell lines. These results indicate that 3-indolyl oxindole substituted isoxazole analogs may be potential lead compounds for further biological screening.

Introduction

Developments of efficient and environmentally benign synthetic methodologies for commonly used small organic molecules are one of the major challenges in modern organic synthesis. Towards this goal, nitrogen containing heterocycles are some of the most representative skeletons in complicated natural products and bioactive molecules.[1] Particularly quaternary centered C-3 functionalized oxindole derivatives are present as a characteristic structural motif in numerous alkaloids[2] that exhibit diverse biological and pharmaceutical activities, such as 3-hydroxy-*N*-methyl welwitindolinone C (1) having an oxindole core and, hence, is a fascinating synthetic target to achieve. The tricyclic core (1) has been reported to be synthesized from 3-hydroxy oxindole derivatives (Fig. 1).

Functionalized indole and its derivative oxindole have attracted much attention from the organic community.[13] Recently, 3-indolylmethanols have distinguished themselves to be versatile reactants in nucleophilic substitutions, leading to C-3 functionalization of indoles.[13–15] Nevertheless, most of the nucleophilic substitions were focussed on alkylation using acyclic and aromatic compounds, which introduced alkyl, alkenyl, allyl, and aryl groups to 3-indolylmethanols (eqn (1)).[14]

In sharp contrast, the nucleophilic reaction of 3-indolylmethanol using cyclic compounds has met with little success (eqn (2)), and only a limited example using electron rich enaminone as the nucleophile was sporadically reported in the literature (Scheme 1).[8] Therefore nucleophilic reactions of 3-indolylmethanol, especially those employing other types of cyclic nucleophiles, are highly desirable.

In addition, 3-hydroxy-2-oxindole especially serves as a versatile building block for the syntheses of many indole based biologically active molecules. Consequently, the 3-substituted-3-hydroxy-2-oxindole framework has been an intensively investigated synthetic target to realize different C–C bonds developed for the synthesis of 3,3-disubstituted oxindole[3a] and in 1998, Olah and co-workers[3b] reported a general synthetic route to

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† Electronic supplementary information (ESI) available: Copies of ^{1}H NMR, and ^{13}C NMR spectra of all compounds and the experimental procedure. CCDC 1063584. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c8nj02276c

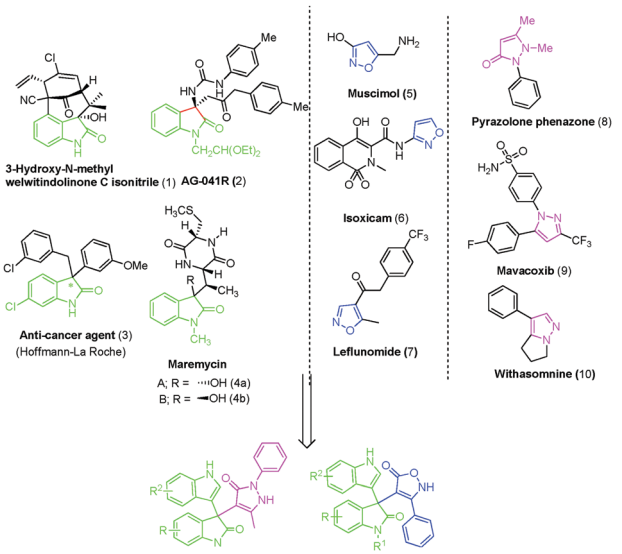


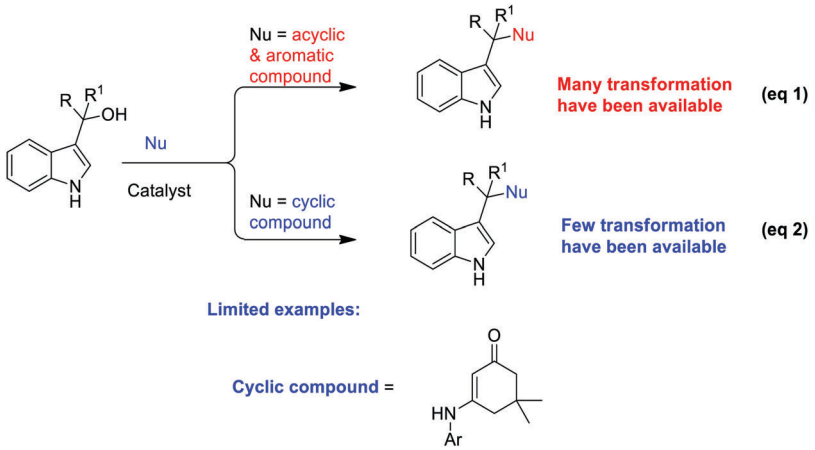
Fig. 1 Biologically active natural products containing oxindole, isoxazole and pyrazole structural frameworks.

symmetrical 3,3-disubstituted oxindoles from isatins in super-acidic triflic acid (CF_3SO_3H, TfOH). Following this report, Halperin,[3c] Zolotukhin,[3d] and Bjorkling[3e] independently reported similar approaches to a variety of symmetrically and unsymmetrically substituted 2-oxindoles. In 2007, Padwa and co-workers,[3f] Zolotukhin,[3d] and Bjorkling[3e] independently reported similar approaches to a variety of symmetrically and unsymmetrically substituted 2-oxindoles. Recently, Zhu and co-workers[3g] have reported a one-pot integrated Brønsted base-catalysed trichoroacetimidation of 3-hydroxyoxindoles followed by a Brønsted acid-catalysed nucleophilic substitution reaction to access a variety of unsymmetrically substituted 2-oxindoles. Although a number of methods for the synthesis of 3,3-disubstituted oxindoles have been developed,[3h–n] more -environmentally benign and efficient approaches are still needed to reduce the use of expensive metal catalysts, solvents, and toxic reagents. Among these, multicomponent reactions are preferred over stepwise synthetic methods for the following advantages: reduced pollutant production, reduced use of toxic and hazardous chemicals, operational simplicity and reduced reaction time, easy isolation of pure products that avoids tedious purification steps, high yields and reduced costs.[4]

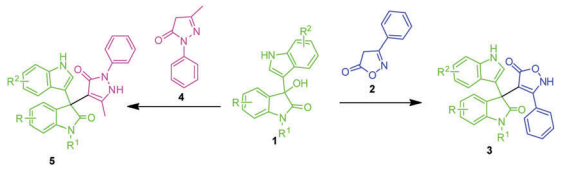
Isoxazoles[5] and pyrazoles[6] represent an interesting class of heterocycles that display a range of biological properties. We presumed that a reasonable assembly of isoxazole, pyrazole and isatin for the syntheses of osoxazole–isatin–pyrazole conjugates will provide a new platform for drug discovery. In continuation of our research work on multicomponent reactions[7a,b] for the synthesis of isoxazole and pyrazole fused heterocycles,[7c] we describe herein the first C-3 functionalisation of isoxazole and pyrazole with 3-substituted-3-hydroxy oxindole in ethanol. This approach provides easy access to highly functionalized isoxazole and pyrazole substituted 3,3-disubstituted-oxindole derivatives (Scheme 2).

Results and discussion

Initial reactions were carried out with 3-hydroxy oxindole **1a** and isoxazolone **2a** leading to the formation of 3,3-disubstituted oxindole **3a** chosen as a model to investigate the feasibility of the strategy and to optimize the reaction conditions (Table 1). To begin with, the reaction was performed in the absence of a Lewis acid in ethanol which failed to yield the product even after 10 h either at ambient temperature or in reflux conditions. This reaction was tested in the presence of Lewis acids (Table 1, entries 1, 2, 4 and 5), a Brønsted acid (Table 1, entry 6) and bifunctional catalysts (Table 1, entries 7–9) in refluxing water, ethanol, methanol, acetonitrile and neat conditions, for different reaction times, and comparable results were obtained in all cases. Interestingly, when *p*-TSA·H_2O was used, the reactivity was much improved (Table 1, entry 3). We also investigated the amount of *p*-TSA·H_2O required for this reaction and it was observed that with a decreasing amount of the catalyst, the yield also decreased (Table 1, entries 10 and 11). A further increase in the catalyst



Scheme 1 Profile for nucleophilic substitutions of 3-indolylmethanol.



Scheme 2 Designed tandem process to form functionalized 3,3-disubstituted oxindole derivatives.

loading from 20 to 25 mol% has no obvious influence on the reaction yield (Table 1, entry 12).

Thus 20 mol% of *p*-TSA·H_2O in ethanol is sufficient to enable the reaction in 5–7 h to afford the product **3a** in a very good yield of 89% (Table 1, entry 3). Subsequently, the effect of solvents was examined.

Several organic solvents, such as CH_3CN, toluene, and H_2O and neat conditions showed no superiority to MeOH. When the same reaction was performed in ethanol, a good yield of the product was observed after 3 h (Table 1, entry 13).

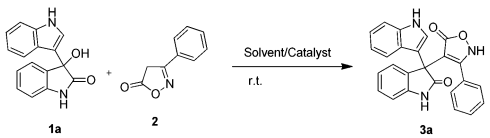
Thus, *p*-TSA·H_2O emerged as the ideal choice of Barnstead acid for these nucleophilic substitution reactions. After completion of the reaction the product was purified by column chromatography to obtain pure **3a** in good yield. To extend our strategy further, we used amino pyrazole **4** instead of isoxazole **2** and 3-hydroxy-3-indolylindolin-2-ones **1** with various substituent groups under similar conditions and the corresponding 3,3-disubstituted oxindoles **5(a–k)** were obtained in high yields (Table 2). Accordingly, we have been able to prepare a library of 4-(3-(1*H*-indole-3-yl)-2-oxoindolin-3-yl)-3-phenylisoxazol-5(4*H*)-one **3(a–n)** and 3-(1*H*-indol-3-yl)-3-(3-methyl-5-oxo-1-phenyl-4,5-dihydro-1*H*-pyrazol-4-yl)-indolin-2-one **5(a–k)** derivatives (Table 2) using 3-hydroxy-3-indolylindolin-2-ones **1** and isoxazoles/pyrazoles **2**/**4** under green conditions. Consequently after completion of the reaction, the product was purified by column chromatography.

In recent years, it has become a popular notion that just because reactions are conducted in sustainable media such as water or lower alcohols it does not mean the method is "green". The environmental impact of a synthetic process is determined by factors such as the efficiency of the reaction, the workup process, and the clean-up and disposal of solvent. As per the synthetic protocol presented in this paper, the reaction was carried out in ethanol using a cheap catalyst with good efficiency. Furthermore, this reaction is a one-step process with a high atom economy and water is afforded as the by-product in this reaction. This approach therefore exemplifies the reconciliation of structural complexity and operational simplicity in an environmentally benign time and cost effective manner (Scheme 3).

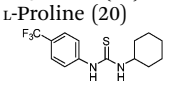
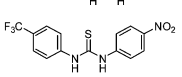
At the outset, we proposed the possible addition of isoxazolone **2** to the reactive 2*H*-indol-2-one **1** to effect the nucleophilic amide nitrogen to form the intermediate **6**. Intermediate **6** would then react with isoxazolone **2** to afford the C-3 functionalished oxindole product **3** *via* Michael addition followed by proton abstraction of the intermediate **3′**. The structures of compounds **3a–n** and **5a–k** were confirmed by ^1H and ^{13}C NMR spectroscopy and mass spectrometry. EI-HRMS of compound **5b** indicated the accurate molecular mass at 498.0690.

The ^1H NMR spectrum of **5b** exhibited broad signals at δ 10.43 and 11.0 (–NH groups) which confirmed the incorporation of indole and oxindole rings in the structure. Resonances at

Table 1 Reaction optimization conditions

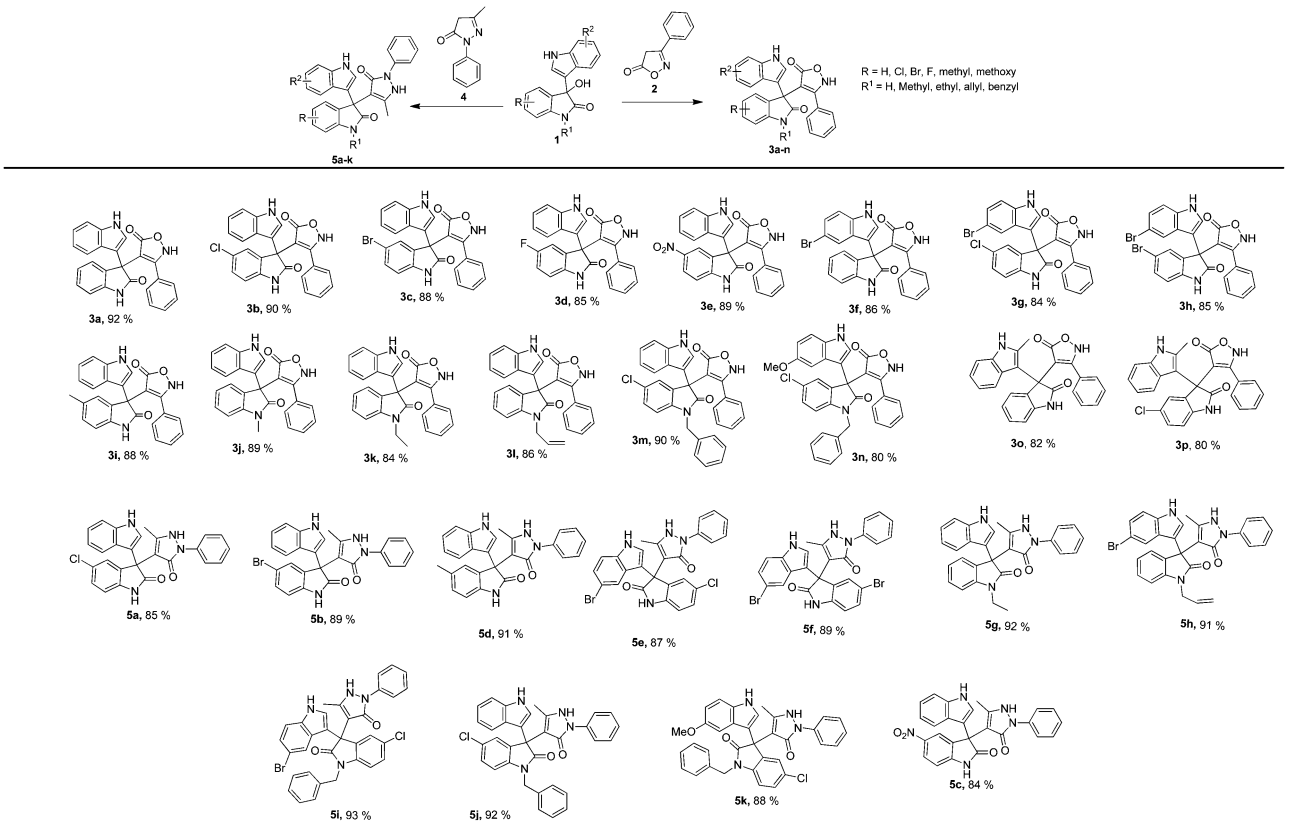


1a 2 3a

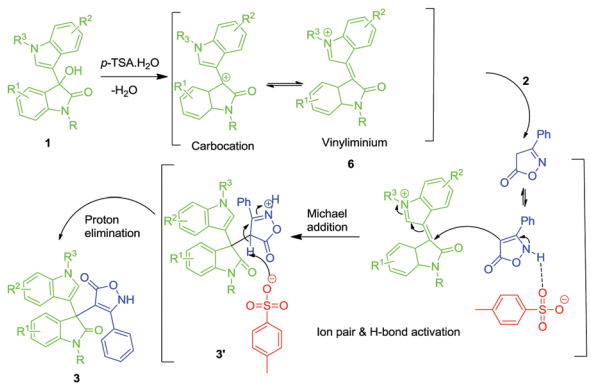
Entry	Catalyst (mol%)	Time (h)	Yield (%) MeOH[a,b]	EtOH[a,b]	CH_3CN[a,b]	Neat[a,b]	H_2O[a,b]
1.	$InCl_3$ (20)	10	—	Trace	Trace	—	—
2.	$SnCl_2·2H_2O$ (20)	10	—	Trace	Trace	—	Trace
3.	*p*-TSA·H_2O (20)	7	60	89	20	20	35
4.	$In(OTf)_3$ (20)	17	10	15	Trace	Trace	—
5.	$Cu(OTf)_2$ (20)	12	—	Trace	10	15	—
6.	CF_3COOH (20)	15	35	50	30	—	20
7.	L-Proline (20)	18	Trace	Trace	Trace	—	—
8.	 (20)	15	10	Trace	Trace	—	—
9.	 (20)	15	15	Trace	Trace	—	—
10.	*p*-TSA·H_2O (15)	4	50	75	20	—	30
11.	*p*-TSA·H_2O (5)	4	30	35	15	—	20
12.	*p*-TSA·H_2O (25)	4	60	89	25	—	35
13.	*p*-TSA·H_2O (20)	3	60	89	15	20	35
14.	*p*-TSA·H_2O (20)	2	50	70	20	15	30
15.	*p*-TSA·H_2O (20)	1	45	67	15	10	25

[a] The reaction was performed with 3-hydroxy-3-indolylindolin-2-ones **1a** (1 mmol), isoxazole **2** (1 mmol) and the catalyst at r.t. [b] Isolated yields after column chromatography.

Table 2 Substrate scope of the synthesis of 3,3-disubstituted oxindole derivatives[a,b,c]



[a] The reaction was performed with 3-hydroxy-3-indolylindolin-2-ones **1a** (1 mmol), isoxazolone **2**/pyrazolone **4** (1 mmol), *p*-TSA·H_2O (0.20 mmol) and ethanol (3 mL), at rt. [b] Reaction progress was followed by TLC analysis. [c] Yield of isolated products.



Scheme 3 Plausible reaction mechanism for the formation of product **3**.

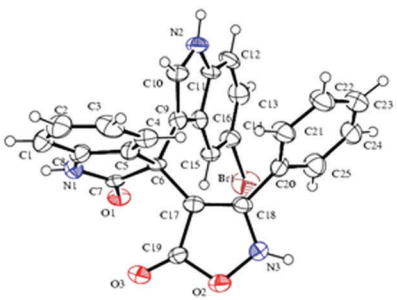


Fig. 2 ORTEP diagram of compound **3f**.

51.3 due to one quaternary carbon and 177.9 (one carbonyl group) are observed in the ^{13}C NMR spectrum. Moreover, the compound **3f** was unambiguously characterized by X-ray crystallography (Fig. 2).[9]

Pharmacology

In the course of identifying various novel anti-microbial and anti-cancer agents, we are particularly interested in the present work with 3,3-disubstituted oxindoles which have been identified as a new class of anti-microbial and anti-cancer agents with significant therapeutic efficacy.

Anti-microbial activity

All 25 compounds were screened for antimicrobial activity against human bacterial pathogens, including the Gram-positive bacterium methicillin resistant *Staphylococcus aureus* (MRSA), the Gram-negative bacteria *Pseudomonas aeruginosa*, *Escherichia coli* and *Klebsiella pneumoniae* and a human yeast pathogen, fluconazole resistant *Candida albicans* (FRCA). The *in vitro* anti-microbial results are summarized in Table 3.

Table 3 Antimicrobial activity of the synthesized compounds against human pathogens

	Zone of inhibition (mm)				
		Gram-negative bacterium			
Compound	Gram-positive bacterium (MRSA)	*P. aeruginosa*	*K. pneumoniae*	*E. coli*	Yeast strain FRCA
3a	18	14	N	N	15
3b	13	15	N	N	17
3c	20	10	N	N	16
3d	24	N	N	N	13
3e	17	9	N	N	17
3f	15	16	N	N	18
3g	27	24	N	N	22
3h	20	18	N	N	19
3i	21	13	N	N	17
3j	N	N	N	N	17
3k	20	13	N	N	21
3l	13	N	N	N	15
3m	26	22	N	N	25
3n	22	17	N	N	23
5a	17	16	N	N	19
5b	14	9	N	N	18
5c	13	10	N	N	17
5d	12	10	N	N	20
5e	11	N	N	N	20
5f	11	13	N	N	21
5g	N	N	N	N	16
5h	N	N	N	N	13
5i	10	11	N	N	16
5j	12	13	N	N	16
5k	10	12	N	N	15
P.C.	N	30	N	N	N
N.C.	N	N	N	N	N

P.C.: Streptomycin 30 μg for MRSA, *P. aeruginosa, K. pneumoniae* and *E. coli*; fluconazole 30 μg for FRCA; negative control (N.C.): 10% DMSO; N: No inhibition.

Compounds **3g** & **3m** showed excellent activity against *P. aeruginosa*, MRSA and *C. albicans*. However there was no activity against *E. coli* and *K. pneumoniae*.

All other tested compounds showed moderate to good activities. The *in vitro* minimum inhibitory concentration (MIC) of the compound against human pathogens was determined by the method of the National Committee for Clinical Laboratory Standards (NCCLS).[10] The MIC values are summarized in Table 4. The standard antibiotics streptomycin and fluconazole were used as controls. The results revealed that the compounds **3g** and **3m** show very good anti-microbial activity against the organisms. All other tested compounds showed moderate to excellent activities.

Cytotoxicity

The compounds **3g** and **3m** were evaluated for cytotoxicity against MCF-7 and Hep-2 cancer cell lines using the commercially available standard drug cisplatin as a positive control.[11] Their IC_{50} concentrations are depicted in Table 5. The results demonstrated that *N*-benzyl oxindole derivative **3m** exhibited higher inhibitory activity compared to N–H oxindole derivative **3g**. The results indicated that 3-isoxazolyl oxindole ring fused 3,3-disubstituted oxindole analogs may be useful leads for further biological screening.

Table 4 Minimum inhibitory concentration of the compounds against human pathogens

	Concentration (μg)				
	Gram-positive bacterium	Gram-negative bacterium			
Entry	MRSA	*P. aeruginosa*	*K. pneumoniae*	*E. coli*	FRCA
3a	250	250	ND	ND	250
3b	500	250	ND	ND	250
3c	62.5	ND	ND	ND	250
3d	125	125	ND	ND	250
3e	125	125	ND	ND	31.25
3f	125	125	ND	ND	125
3g	250	62.5	ND	ND	62.5
3h	125	125	ND	ND	110
3i	125	125	ND	ND	90
3j	ND	ND	ND	ND	125
3k	125	125	ND	ND	62.5
3l	15.625	ND	ND	ND	15.62
3m	7.8123	15.625	ND	ND	62.5
3n	250	500	ND	ND	62.5
5a	125	125	ND	ND	62.5
5b	125	125	ND	ND	62.5
5c	125	125	ND	ND	125
5d	500	500	ND	ND	250
5e	500	500	ND	ND	62.5
5f	250	250	ND	ND	500
5g	ND	ND	ND	ND	31.25
5h	ND	ND	ND	ND	125
5i	ND	ND	ND	ND	250
5j	125	125	ND	ND	250
5k	125	125	ND	ND	125
P.C.	ND	3.90	ND	ND	ND
N.C.	ND	ND	ND	ND	ND

ND: Not determined as they did not show antimicrobial activity in the well diffusion assay.

Table 5 IC_{50} values of compounds against human cancer cell lines

	IC_{50} (μg mL^{-1})		
Compound	Hep-2	MCF-7	Vero cells
3g	22.09	54.3	123.2
3m	30.04	45.02	150.2

Conclusions

In summary, we have developed an efficient, atom economic and environmentally-benign method for C-3 functionalization of 3-hydroxy oxindoles to produce 3,3-disubstituted oxindoles. The protocol involves addition of isoxazolone/pyrazolone to 3-hydroxy oxindoles with *p*-TSA·H_2O as the catalyst under mild conditions, affording a range of 3,3-disubstituted oxindoles in good to excellent yields. A wide variety of 3,3-disubstituted-oxindoles have been synthesized utilizing our methodology. We anticipate the utility of this transformation to access biologically relevant oxindoles. It is noteworthy that some of these heterocycles exhibit promising anti-microbial and anti-cancer activities. Further mechanistic studies, synthetic applications, and efforts towards the asymmetric version are currently in progress in our laboratory.

Experimental

Materials and methods

All chemicals were purchased from Sigma Aldrich. All melting points are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded in DMSO-d_6 using TMS as an internal standard with a Bruker Avance spectrometer at 400 MHz amd 100 MHz, respectively. Mass spectra were recorded using a JEOL GCMate-II–HR mass spectrometer. Analytical TLC was performed on precoated aluminium sheets of siliga gel G/UV-254 of 0.2 mm thickness (Merck, Germany).

Starting materials

3-Hydroxy oxindoles **1** were prepared according to the literature procedure.[12]

General procedure for the synthesis of 4-(3-(1*H*-indol-3-yl)-2-oxoindolin-3-yl)-3-phenylisoxazol-5(4*H*)-one (3a–n) and 3-(1*H*-indol-3-yl)-3-(3-methyl-5-oxo-1-phenyl-4,5-dihydro-1*H*-pyrazol-4-yl)indolin-2-one derivatives (5a–k). A mixture of 3-hydroxy-3-indolylindolin-2-ones, **1** (1 mmol), isoxazole/pyrazole **2**/**4** (1 mmole) and *p*-TSA·H_2O (0.20 mmol) in ethanol (3 mL) was stirred at room temperature for 2–4 h. The crude products were purified by column chromatography (5 : 95% MeOH/$CHCl_3$) to obtain pure **3a–n** and **5a–k** in good yields (80–94%). The identities of products **3a–n** and **5a–k** were confirmed by NMR and EI-HRMS, giving good agreement with the assigned structures.

3a: 4-(3-(1*H*-Indol-3-yl)-2-oxoindolin-3-yl)-3-phenylisoxazol-5(2*H*)-one. Isolated as a white solid, 92%, m.p.: 214–216 °C, ^{1}H NMR (400 MHz, DMSO-d_6): δ_H 12.45 (1H, s), 10.69 (1H, s), 10.60 (1H, s), 7.53 (1H, d, J = 8.0), 7.44 (1H, s), 7.30 (1H, dd, J = 8.3, 2.1), 7.08 (4H, dd, J = 20.2, 13.9), 7.02 (1H, d, J = 8.0), 6.91 (4H, dd, J = 20.5, 15.1), 6.79 (1H, t, J = 7.5), 6.59 (1H, d, J = 2.5) ppm. ^{13}C NMR (100 MHz, DMSO-d_6): δ_C 177.2, 170.8, 164.8, 141.2, 137.1, 135.2, 130.0, 128.5, 128.0, 127.0, 125.8, 125.6, 124.7, 124.0, 121.8, 121.3, 118.6, 111.6, 111.5, 50.9 ppm. EI-HRMS: anal. calcd for $C_{25}H_{17}N_3O_3$: 407.1270, found: 407.1270.

3b: 4-(5-Chloro-3-(1*H*-indol-3-yl)-2-oxoindolin-3-yl)-3-phenylisoxazol-5(2*H*)-one. Isolated as a white solid, 90%, m.p.: 218–220 °C, ^{1}H NMR (400 MHz, DMSO-d_6): δ_H 10.61 (1H, s), 10.37 (1H, s), 7.57 (1H, d, J = 7.5), 7.48 (1H, d, J = 7.0), 7.27 (1H, t, J = 7.7), 7.08 (3H, d, J = 7.8), 6.99 (1H, d, J = 8.0), 6.92 (3H, dd, J = 16.7, 8.6), 6.85 (1H, dd, J = 10.6, 4.0), 6.77 (1H, t, J = 7.4), 6.46 (1H, s) ppm. ^{13}C NMR (100 MHz, DMSO-d_6): δ_C 177.5, 170.8, 164.7, 142.5, 137.1, 132.9, 129.9, 128.6, 127.8, 127.7, 127.5, 127.3, 127.0, 125.9, 125.8, 125.0, 124.0, 122.2, 121.8, 121.1, 118.3, 112.4, 111.4, 110.0, 50.6 ppm. EI-HRMS: anal. calcd for $C_{25}H_{16}ClN_3O_3$: 441.0880, found: 441.0880.

3c: 4-(5-Bromo-3-(1*H*-indol-3-yl)-2-oxoindolin-3-yl)-3-phenylisoxazol-5(2*H*)-one. Isolated as a white solid, 88%, m.p.: 230–231 °C, ^{1}H NMR (400 MHz, DMSO-d_6): δ_H 12.46 (1H, s), 10.71 (1H, s), 10.62 (1H, s), 7.53 (2H, d, J = 12.9), 7.44 (1H, d, J = 7.6), 7.11 (3H, d, J = 4.8), 7.04 (1H, d, J = 7.6), 6.97 (2H, d, J = 6.7), 6.87 (2H, d, J = 7.3), 6.81 (1H, d, J = 7.1), 6.60 (1H, s) ppm. ^{13}C NMR (100 MHz, DMSO-d_6): δ_C 177.1, 170.7, 164.7, 141.6, 137.1, 135.5, 131.3, 130.0, 127.9, 127.4, 127.1, 125.6, 124.0, 121.7, 121.3, 118.6, 113.5, 112.0, 111.7, 111.6, 50.9 ppm. EI-HRMS: anal. calcd for $C_{25}H_{16}$ Br N_3O_3: 485.0375, found: 485.0373.

3d: 4-(5-Fluoro-3-(1*H*-indol-3-yl)-2-oxoindolin-3-yl)-3-phenylisoxazol-5(2*H*)-one. Isolated as a white solid, 85%, m.p.: 220–222 °C, ^{1}H NMR (400 MHz, DMSO-d_6): δ_H 10.68 (1H, s), 10.48 (1H, s), 7.56 (1H, d, J = 7.8), 7.31 (1H, d, J = 7.5), 7.12 (4H, d, J = 6.9), 7.02 (1H, d, J = 7.8), 6.98–6.83 (4H, m), 6.81 (1H, d, J = 7.6), 6.60 (1H, s) ppm. ^{13}C NMR (100 MHz, DMSO-d_6): δ_C 177.5, 170.7, 164.8, 159.4, 157.1, 138.5, 137.1, 134.7, 129.9, 128.0, 127.0, 125.6, 124.0, 121.9, 121.2, 118.5, 114.9, 114.6, 112.7, 112.5, 111.9, 111.5, 110.7, 51.2 ppm. EI-HRMS: anal. calcd for $C_{25}H_{16}FN_3O_3$: 425.1176, found: 425.1173.

3e: 4-(3-(1*H*-Indol-3-yl)-5-nitro-2-oxoindolin-3-yl)-3-phenylisoxazol-5(2*H*)-one. Isolated as a white solid, 89%, m.p.: 192–194 °C, ^{1}H NMR (400 MHz, DMSO-d_6): δ_H 11.20 (1H, s), 10.78 (1H, d, J = 2.1), 8.31–8.14 (2H, m), 7.57 (1H, d, J = 7.9), 7.15–7.08 (4H, m), 7.05 (1H, d, J = 8.0), 6.98 (2H, t, J = 7.7), 6.89 (1H, dd, J = 10.9, 3.9), 6.83 (1H, t, J = 7.5), 6.70 (1H, d, J = 2.6). ^{13}C NMR (100 MHz, DMSO-d_6): δ_C 177.7, 170.7, 164.7, 148.7, 142.6, 137.2, 133.9, 130.1, 127.9, 127.2, 126.1, 125.5, 124.2, 121.6, 121.4, 120.3, 118.8, 111.7, 110.9, 110.2, 50.6 ppm. EI-HRMS: anal. calcd for $C_{25}H_{16}N_4O_5$: 452.1121, found: 452.1120.

3f: 4-(3-(5-Bromo-1*H*-indol-3-yl)-2-oxoindolin-3-yl)-3-phenylisoxazol-5(2*H*)-one. Isolated as a white solid, 86%, m.p.: 210–212 °C, ^{1}H NMR (400 MHz, DMSO-d_6): δ_H 10.85 (1H, d, J = 2.2), 10.41 (1H, s), 7.73 (1H, s), 7.73 (1H, s), 7.49 (1H, d, J = 7.3), 7.30 (2H, td, J = 7.7, 0.9), 7.13–7.07 (2H, m), 7.05 (4H, dd, J = 8.2, 4.1), 6.93 (1H, q, J = 7.6), 6.48 (1H, d, J = 2.6) ppm. ^{13}C NMR (100 MHz, DMSO-d_6): δ_C (100 MHz, DMSO) 177.5, 170.7, 164.6, 142.7, 135.8, 132.2, 129.9, 128.9, 127.7, 127.6, 126.9, 125.7, 125.1, 124.6, 123.6, 122.0, 113.4, 112.0, 111.3, 110.2, 50.5 ppm. EI-HRMS: anal. calcd for $C_{25}H_{16}BrN_3O_3$: 485.0375, found: 485.0373.

3g: 4-(3-(5-Bromo-1*H*-indol-3-yl)-5-chloro-2-oxoindolin-3-yl)-3-phenylisoxazol-5-(2*H*)-one. Isolated as a white solid, 84%, m.p.: 211–213 °C, ^{1}H NMR (400 MHz, DMSO-d_6): δ_H 10.93 (1H, s), 10.59 (1H, s), 7.70 (1H, s), 7.47 (1H, s), 7.35 (1H, dd, J = 8.3, 2.1), 7.12–7.02 (3H, m), 6.94 (5H, dd, J = 15.1, 7.8), 6.60 (1H, d, J = 2.6) ppm. ^{13}C NMR (100 MHz, DMSO-d_6): δ_C 177.2, 170.6, 164.5, 141.5, 135.8, 130.0, 128.8, 127.8, 127.4, 127.0, 126.0, 125.8, 124.9, 124.4, 123.7, 113.5, 111.6, 111.4, 111.2, 50.8 ppm. EI-HRMS: anal. calcd for $C_{25}H_{15}BrClN_3O_3$: 518.9985, found: 518.9984.

3h: 4-(5-Bromo-3-(5-bromo-1*H*-indol-3-yl)-2-oxoindolin-3-yl)-3-phenylisoxazol-5(2*H*)-one. Isolated as a white solid, 85%, m.p.: 220–222 °C, ^{1}H NMR (400 MHz, DMSO-d_6): δ_H 10.92 (1H, s), 10.60 (1H, s), 7.69 (2H, s), 7.57 (1H, s), 7.48 (1H, dd, J = 8.2, 1.7), 7.07 (3H, dd, J = 18.8, 7.3), 6.96 (4H, t, J = 7.3), 6.88 (1H, d, J = 8.2), 6.60 (1H, d, J = 2.5) ppm. ^{13}C NMR (100 MHz, DMSO-d_6): δ_C 177.1, 170.6, 164.5, 141.9, 135.8, 131.7, 127.8, 127.5, 127.4, 127.0, 125.7, 124.4, 123.7, 113.6, 113.5, 112.2, 111.4, 50.8 ppm. EI-HRMS: anal. calcd for $C_{25}H_{15}Br_2N_3O_3$: 562.9480, found: 562.9480.

3i: 4-(3-(1*H*-Indol-3-yl)-5-methyl-2-oxo-indolin-3-yl)-3-phenylisoxazol-5(2*H*)-one. Isolated as a white solid, 88%, m.p.: 228–230 °C, ^{1}H NMR (400 MHz, DMSO-d_6): δ_H 10.61 (d, J = 2.1 Hz, 1H), 10.26 (s, 1H), 7.56 (d, J = 8.0 Hz, 1H), 7.26 (s, 1H), 7.16–7.03 (m, 4H), 7.01 (d, J = 8.1 Hz, 1H), 6.95 (t, J = 7.7 Hz, 2H),

6.84 (dd, J = 11.1, 4.1 Hz, 1H), 6.82–6.75 (m, 2H), 6.48 (d, J = 2.5 Hz, 1H), 2.31 (s, 3H) ppm. ^{13}C NMR (100 MHz, DMSO-d_6): δ_C 177.4, 170.9, 164.6, 140.0, 137.1, 133.0, 130.6, 129.9, 128.9, 128.5, 127.9, 127.0, 125.9, 125.9, 125.5, 124.1, 122.2, 121.1, 118.3, 112.6, 111.4, 109.8, 50.7, 21.3 ppm. EI-HRMS: anal. calcd for $C_{26}H_{19}N_3O_3$: 421.1426, found: 421.1424.

3j: 4-(5′-Bromo-1-methyl-2-oxo-[3,3′-bi-indolin]-3-yl)-3-phenyl-isoxazol-5(2*H*)-one. Isolated as a white solid, 89%, m.p.: 204–207 °C, ^{1}H NMR (400 MHz, DMSO-d_6): δ_H 10.67 (1H, s), 7.56 (2H, d, J = 7.9), 7.39 (1H, t, J = 7.5), 7.16 (2H, d, J = 7.4), 7.12–6.99 (5H, m), 6.92–6.84 (1H, m), 6.79 (1H, d, J = 7.3), 6.47 (1H, d, J = 2.3), 2.97 (3H, s) ppm. ^{13}C NMR (100 MHz, DMSO-d_6): δ_C 175.4, 170.8, 167.0, 143.6, 137.2, 129.5, 128.9, 128.5, 128.2, 127.9, 127.3, 125.9, 124.8, 124.1, 122.7, 122.0, 121.2, 118.4, 111.5, 109.1, 50.0, 26.5 ppm. EI-HRMS: anal. calcd for $C_{26}H_{20}BrN_3O_3$: 501.0688, found: 501.0685.

3k: 4-(3-(1*H*-Indol-3-yl)-1-methyl-2-oxoindolin-3-yl)-3-phenyl-isoxazol-5(2*H*)-one. Isolated as a white solid, 84%, m.p.: 217–219 °C, ^{1}H NMR (400 MHz, DMSO-d_6): δ_H 10.89 (1H, s), 7.76 (1H, s), 7.57 (1H, d, J = 6.8), 7.41 (1H, d, J = 7.3), 7.18 (4H, dd, J = 17.3, 9.6), 7.00 (6H, d, J = 9.4), 6.51 (1H, s), 2.98 (3H, s) ppm. ^{13}C NMR (100 MHz, DMSO-d_6): δ_C 175.6, 170.6, 164.2, 143.9, 137.6, 135.9, 133.3, 131.6, 130.1, 129.1, 128.6, 128.3, 127.8, 127.6, 127.2, 125.8, 124.9, 124.5, 123.7, 122.8, 114.4, 113.5, 111.6, 111.4, 109.2, 49.9, 26.6 ppm. EI-HRMS: anal. calcd for $C_{26}H_{19}N_3O_3$: 421.1426, found: 421.1422.

3l: 4-(1-Allyl-3-(1*H*-indol-3-yl)-2-oxoindolin-3-yl)-3-phenylisoxazol-5(2*H*)-one. Isolated as a white solid, 86%, m.p.: 230–232 °C, ^{1}H NMR (400 MHz, DMSO-d_6): δ_H 10.65 (1H, s), 7.57 (2H, t, J = 7.8), 7.34 (1H, t, J = 7.5), 7.16–7.04 (4H, m), 7.04–6.93 (4H, m), 6.86 (1H, t, J = 7.5), 6.79 (1H, t, J = 7.4), 6.48 (1H, d, J = 2.1), 5.82–5.65 (1H, m), 5.10 (2H, dd, J = 36.5, 13.9), 4.26–4.09 (2H, m) ppm. ^{13}C NMR (100 MHz, DMSO-d_6): δ_C 175.5, 170.7, 164.6, 142.8, 137.2, 132.3, 132.2, 129.9, 128.6, 127.9, 127.1, 125.8, 124.8, 124.0, 122.6, 122.1, 121.2, 118.5, 117.0, 112.2, 111.5, 109.7, 50.2, 42.1 ppm. EI-HRMS: anal. calcd for $C_{28}H_{21}N_3O_3$: 447.1583, found: 447.1580.

3m: 4-(1-Benzyl-5-chloro-3-(1*H*-indol-3-yl)-2-oxoindolin-3-yl)-3-phenylisoxazol-5(2*H*)-one. Isolated as a white solid, 90%, m.p.: 215–217 °C, ^{1}H NMR (400 MHz, DMSO-d_6): δ_H 10.74 (1H, d, J = 1.8), 7.54 (2H, dd, J = 11.5, 4.7), 7.28 (6H, dd, J = 23.9, 12.0), 7.11 (3H, d, J = 7.8), 7.03 (1H, d, J = 8.0), 6.96 (2H, t, J = 7.7), 6.88 (2H, t, J = 8.7), 6.81 (1H, t, J = 7.3), 6.61 (1H, d, J = 2.5), 4.84 (2H, dd, J = 55.0, 16.1) ppm. ^{13}C NMR (100 MHz, DMSO-d_6): δ_C 175.6, 170.6, 164.7, 141.5, 137.1, 136.3, 134.3, 130.0, 129.0, 128.9, 128.5, 128.0, 127.7, 127.4, 127.1, 126.8, 125.9, 125.6, 124.7, 124.1, 121.7, 121.4, 118.7, 111.7, 111.4, 111.2, 50.5, 43.5 ppm. EI-HRMS: anal. calcd for $C_{32}H_{22}ClN_3O_3$: 531.1350, found: 531.1350.

3n: 4-(1-Benzyl-5-chloro-3-(5-methoxy-1*H*-indol-3-yl)-2-oxoindolin-3-yl)-3-phenyl-isoxazol-5(2*H*)-one. Isolated as a white solid, 80%, m.p.: 218–220 °C, ^{1}H NMR (400 MHz, DMSO-d_6): δ_H 10.62 (1H, d, J = 2.0), 7.55 (1H, s), 7.28 (6H, dd, J = 16.0, 11.9), 7.13 (3H, d, J = 7.1), 6.98 (3H, t, J = 7.5), 6.89 (2H, d, J = 8.5), 6.57 (1H, d, J = 2.5), 6.54 (1H, dd, J = 8.8, 2.0), 4.84 (2H, dd, J = 61.2, 16.2), 3.66 (3H, s) ppm. ^{13}C NMR (100 MHz, DMSO-d_6): δ_C 175.6, 170.8, 164.8, 153.0, 141.6, 136.3, 134.2, 132.3, 130.1, 128.9, 128.5, 127.9, 127.7, 127.4, 127.1, 126.8, 125.9, 124.8, 124.7, 112.2, 111.6, 111.2, 110.8, 103.8, 55.7, 50.6, 43.4 ppm. EI-HRMS: anal. calcd for $C_{33}H_{24}ClN_3O_4$: 561.1455, found: 561.1453.

3o: 4-(3-(2-Methyl-1*H*-indol-3-yl)-2-oxoindolin-3-yl)-3-phenyl-isoxazol-5(2*H*)-one. Isolated as a white solid, 82%, m.p.: 204–206 °C, ^{1}H NMR (400 MHz, DMSO-d_6): δ_H 10.87 (1H, s), 10.51 (1H, d, J = 10.4), 7.78–7.34 (2H, m), 7.25 (4H, dd, J = 50.4, 22.2), 6.92 (4H, dd, J = 24.1, 17.5), 6.77–6.55 (3H, m), 2.01 (3H, d, J = 53.7) ppm. ^{13}C NMR (100 MHz, DMSO-d_6): δ_C 179.8, 178.3, 170.7, 142.2, 141.6, 136.0, 135.4, 135.3, 135.1, 134.3, 132.4, 130.4, 129.5, 128.2, 128.1, 127.9, 127.5, 127.2, 125.9, 125.3, 121.7, 120.2, 120.0, 119.8, 118.3, 118.1, 110.8, 109.9, 52.9, 13.6, 13.4 ppm. EI-HRMS: anal. calcd for $C_{26}H_{19}N_3O_3$: 421.1426, found: 421.1420.

3p: 4-(5-Chloro-3-(2-methyl-1*H*-indol-3-yl)-2-oxoindolin-3-yl)-3-phenylisoxazol-5(2*H*)-one. Isolated as a white solid, 80%, m.p.: 225–227 °C, ^{1}H NMR (400 MHz, DMSO-d_6): δ_H 10.95 (1H, d, J = 14.3), 10.72 (1H, s), 10.55 (1H, s), 7.52–7.24 (5H, m), 7.17 (2H, d, J = 7.0), 6.99 (3H, dd, J = 24.5, 15.4), 6.87–6.61 (2H, m), 2.09 (3H, s) ppm. ^{13}C NMR (100 MHz, DMSO-d_6): δ_c 179.4, 178.0, 170.5, 164.8, 140.7, 140.5, 138.0, 136.3, 135.4, 135.1, 135.0, 132.5, 128.2, 128.1, 128.0, 127.9, 127.8, 127.1, 125.9, 125.7, 125.7, 124.6, 120.3, 119.6, 118.7, 111.4, 111.0, 53.2, 13.3 ppm. EI-HRMS: anal. calcd for $C_{26}H_{18}ClN_3O_3$: 455.1037, found: 455.1033.

5a: 5-Chloro-3-(1*H*-indol-3-yl)-3-(5-methyl-3-oxo-2-phenyl-2,3-dihydro-1*H*-pyrazol-4-yl)indolin-2-one. Isolated as a white solid, 85%, m.p.: 202–204 °C, ^{1}H NMR (400 MHz, DMSO-d_6): δ_H 10.99 (1H, s), 10.38 (1H, s), 7.79 (1H, s), 7.69 (2H, d, J = 8.0), 7.49–7.35 (3H, m), 7.28 (2H, d, J = 5.0), 7.18 (1H, d, J = 6.8), 7.09 (1H, t, J = 7.5), 7.01–6.84 (2H, m), 6.67 (1H, s), 1.53 (3H, s) ppm. ^{13}C NMR (100 MHz, DMSO-d_6): δ_C 177.9, 149.2, 141.7, 137.5, 135.8, 129.3, 128.1, 126.5, 125.4, 124.8, 124.0, 122.2, 121.8, 119.0, 118.4, 112.8, 112.1, 111.1, 51.3, 25.5 ppm. EI-HRMS: anal. calcd for $C_{26}H_{19}ClN_4O_2$: 454.1197, found: 454.1195.

5b: 5-Bromo-3-(1*H*-indol-3-yl)-3-(5-methyl-3-oxo-2-phenyl-2,3-dihydro-1*H*-pyrazol-4-yl)indolin-2-one. Isolated as a white solid, 89%, m.p.: 208–210 °C, ^{1}H NMR (400 MHz, DMSO-d_6): δ_H 11.02 (1H, s), 10.44 (1H, s), 7.81–7.66 (3H, m), 7.40 (5H, s), 7.14 (2H, d, J = 30.5), 7.01–6.79 (2H, m), 6.68 (1H, s), 1.54 (3H, s) ppm. ^{13}C NMR (100 MHz, DMSO-d_6): δ_C 177.9, 148.9, 142.0, 137.6, 137.5, 136.2, 131.0, 129.3, 127.6, 126.5, 124.9, 124.0, 122.2, 121.8, 119.0, 118.8, 113.2, 112.9, 112.2, 111.7, 51.3, 25.6 ppm. EI-HRMS: anal. calcd for $C_{26}H_{19}BrN_4O_2$: 498.0691, found: 498.0690.

5c: 3-(1*H*-Indol-3-yl)-3-(5-methyl-3-oxo-2-phenyl-2,3-dihydro-1*H*-pyrazol-4-yl)-5-nitroindolin-2-one. Isolated as a white solid, 84%, m.p.: 222–224 °C, ^{1}H NMR (400 MHz, DMSO-d_6): δ_H 11.10 (1H, s), 11.02 (1H, s), 8.23 (1H, dd, J = 8.6, 2.1), 8.02 (1H, s), 7.81 (1H, d, J = 8.0), 7.69 (1H, d, J = 7.9), 7.49 (1H, s), 7.41 (3H, s), 7.18 (1H, d, J = 7.2), 7.10 (2H, dd, J = 18.2, 8.0), 7.00–6.92 (1H, m), 6.79 (1H, d, J = 2.1), 1.54 (3H, s) ppm. ^{13}C NMR (100 MHz, DMSO-d_6): δ_C 178.5, 149.3, 149.0, 142.3, 137.6, 137.4, 134.6, 129.3, 128.5, 126.4, 125.9, 125.0, 124.3, 122.0, 120.9, 120.3, 119.2, 118.8, 112.3, 111.9, 109.8, 51.0, 25.5 ppm. EI-HRMS: anal. calcd for $C_{26}H_{19}N_5O_4$: 465.1437, found: 465.1435.

5d: 3-(6-Methyl-1*H*-indol-3-yl)-3-(5-methyl-3-oxo-2-phenyl-2,3-dihydro-1*H*-pyrazol-4-yl)indolin-2-one. Isolated as a white solid, 89%, m.p.: 192–194 °C, ^{1}H NMR (400 MHz, DMSO-d_6): δ_H 10.94 (1H, d, J = 1.8), 10.15 (1H, s), 7.76 (1H, d, J = 7.8), 7.70 (2H, d, J = 7.8), 7.39 (3H, dd, J = 16.9, 8.4), 7.16 (1H, t, J = 7.4), 7.1–6.99 (3H, m), 6.92 (1H, t, J = 7.6), 6.77 (1H, d, J = 7.7), 6.62 (1H, d, J = 2.2), 2.27 (s, 3H), 1.53 (3H, s) ppm. ^{13}C NMR (100 MHz, DMSO-d_6): δ_C 178.3, 148.8, 140.2, 137.8, 137.5, 133.8, 130.2, 129.3, 128.5, 126.7, 125.6, 124.8, 124.1, 122.4, 121.6, 118.8, 113.8, 112.0, 109.4, 51.0, 25.5, 12.3 ppm. EI-HRMS: anal. calcd for $C_{27}H_{22}N_4O_2$: 434.1743, found: 434.1740.

5e: 3-(5-Bromo-1*H*-indol-3-yl)-5-chloro-3-(5-methyl-3-oxo-2-phenyl-2,3-dihydro-1*H*-pyrazol-4-yl)indolin-2-one. Isolated as a white solid, 91%, m.p.: 210–211 °C, ^{1}H NMR (400 MHz, DMSO-d_6): δ_H 11.00 (1H, s), 10.30 (1H, s), 7.75 (1H, d, J = 7.5), 7.70 (2H, d, J = 7.9), 7.40 (3H, dd, J = 14.7, 7.7), 7.20–7.11 (2H, m), 7.11–7.04 (1H, m), 6.94 (1H, t, J = 7.5), 6.86 (1H, dd, J = 8.4, 4.4), 6.69 (1H, d, J = 1.9), 1.54 (3H, s) ppm. ^{13}C NMR (100 MHz, DMSO-d_6): δ_C 178.3, 159.3, 157.0, 138.8, 137.7, 137.5, 135.5, 135.5, 129.3, 126.5, 124.9, 124.0, 122.2, 121.7, 118.9, 118.8, 114.5, 114.3, 113.1, 112.8, 112.6, 112.1, 110.3, 110.3, 51.5, 25.5 ppm. EI-HRMS: anal. calcd for $C_{26}H_{18}BrClN_4O_2$: 532.0302, found: 532.0301.

5f: 5-Bromo-3-(5-bromo-1*H*-indol-3-yl)-3-(5-methyl-3-oxo-2-phenyl-2,3-di-hydro-1*H*-pyrazol-4-yl)indolin-2-one. Isolated as a white solid, 87%, m.p.: 218–220 °C, ^{1}H NMR (400 MHz, DMSO-d_6): δ_H 11.24 (1H, s), 10.47 (1H, s), 7.95 (1H, s), 7.69 (2H, d, J = 5.8), 7.40 (5H, d, J = 9.5), 7.20 (2H, s), 6.86 (1H, s), 6.73 (1H, s), 1.52 (3H, s) ppm. ^{13}C NMR (100 MHz, DMSO-d_6): δ_C 177.8, 148.7, 142.0, 137.5, 136.3, 135.7, 131.3, 129.3, 128.5, 128.2, 127.6, 125.9, 125.8, 125.0, 124.4, 124.2, 118.8, 114.3, 113.3, 112.5, 111.8, 111.7, 105.7, 51.1, 25.5 ppm. EI-HRMS: anal. calcd for $C_{26}H_{18}Br_2N_4O_2$: 575.9797, found: 575.9795.

5g: 3-(1*H*-Indol-3-yl)-1-methyl-3-(5-methyl-3-oxo-2-phenyl-2,3-dihydro-1*H*-pyrazol-4-yl)indolin-2-one. Isolated as a white solid, 92%, m.p.: 212–214 °C, ^{1}H NMR (400 MHz, DMSO-d_6): δ_H 11.22 (1H, s), 8.02 (1H, s), 7.67 (2H, d, J = 7.9), 7.43–7.28 (5H, m), 7.25–7.00 (5H, m), 6.67 (1H, d, J = 2.4), 3.0 (3H, s), 1.51 (3H, s). ^{13}C NMR (100 MHz, DMSO-d_6): δ_C 176.5, 148.5, 144.1, 138.2, 137.5, 136.3, 132.3, 129.4, 129.3, 128.6, 128.5, 128.3, 125.9, 125.8, 124.9, 124.7, 124.4, 124.4, 122.3, 118.8, 114.2, 112.8, 111.6, 108.8, 106.5, 50.3, 26.6, 21.2 ppm. EI-HRMS: anal. calcd for $C_{27}H_{22}N_4O_2$: 434.1743, found: 434.1740.

5h: 1-Allyl-3-(5-bromo-1*H*-indol-3-yl)-3-(5-methyl-3-oxo-2-phenyl-2,3-dihydro-1*H*-pyrazol-4-yl)indolin-2-one. Isolated as a white solid, 91%, m.p.: 200–202 °C, ^{1}H NMR (400 MHz, DMSO-d_6): δ_H 11.22 (1H, d, J = 1.7), 8.03 (1H, s), 7.68 (2H, d, J = 7.9), 7.39 (3H, dd, J = 15.7, 8.1), 7.30 (2H, dd, J = 11.7, 7.5), 7.22 (1H, dd, J = 8.6, 1.8), 7.16 (1H, t, J = 7.4), 7.08 (1H, d, J = 7.5), 6.95 (1H, d, J = 7.8), 6.68 (1H, d, J = 2.4), 5.82 (1H, dd, J = 11.2, 6.0), 5.16 (2H, dd, J = 13.8, 11.4), 4.35–4.22 (2H, m), 4.27–4.21 (1H, s), 1.52 (3H, s) ppm. ^{13}C NMR (100 MHz, DMSO-d_6): δ_C 176.2, 148.6, 143.1, 137.5, 136.3, 132.6, 132.4, 129.3, 128.6, 128.5, 128.3, 125.9, 125.7, 125.0, 124.8, 124.4, 124.4, 122.3, 118.9, 117.2, 114.3, 113.1, 111.7, 109.5, 106.4, 50.4, 42.1, 21.2 ppm. EI-HRMS: anal. calcd for $C_{29}H_{23}BrN_4O_2$: 538.1004, found: 538.1003.

5i: 1-Benzyl-3-(5-bromo-1*H*-indol-3-yl)-5-chloro-3-(5-methyl-3-oxo-2-phenyl-2,3-dihydro-1*H*-pyrazol-4-yl)indolin-2-one. Isolated as a white solid, 93%, m.p.: 182–184 °C, ^{1}H NMR (400 MHz, DMSO-d_6): δ_H 11.30 (1H, s), 8.03 (1H, s), 7.72 (2H, d, J = 7.9), 7.53–7.35 (6H, m), 7.24 (6H, dd, J = 15.3, 11.8), 6.83 (1H, d, J = 8.4), 6.76 (1H, d, J = 2.1), 4.88 (2H, dd, J = 28.1, 16.1), 1.50 (3H, s) ppm. ^{13}C NMR (100 MHz, DMSO-d_6): δ_C 176.2, 148.8, 142.0, 137.4, 136.6, 136.4, 134.4, 129.4, 128.9, 128.5, 128.4, 128.2, 127.6, 127.5, 126.6, 125.9, 125.1, 124.9, 124.5, 124.3, 119.0, 114.4, 112.2, 111.8, 110.9, 105.4, 50.7, 43.5, 25.3 ppm. EI-HRMS: anal. calcd for $C_{33}H_{24}BrClN_4O_2$: 622.0771, found: 622.0770.

5j: 1-Benzyl-5-chloro-3-(1*H*-indol-3-yl)-3-(5-methyl-3-oxo-2-phenyl-2,3-dihydro-1*H*-pyrazol-4-yl)indolin-2-one. Isolated as a white solid, 92%, m.p.: 180–182 °C, ^{1}H NMR (400 MHz, DMSO-d_6): δ_H 11.06 (1H, s), 7.81 (1H, d, J = 8.0), 7.71 (1H, d, J = 7.9), 7.50 (1H, d, J = 8.0), 7.44–7.38 (3H, m), 7.35 (2H, d, J = 5.5), 7.28–7.18 (5H, m), 7.15–7.07 (2H, m), 6.96 (1H, t, J = 7.5), 6.81 (1H, d, J = 8.4), 6.68 (1H, d, J = 2.3), 4.46 (2H, s), 3.60 (1H, t, J = 6.4), 1.52 (3H, s) ppm. ^{13}C NMR (100 MHz, DMSO-d_6): δ_C 176.3, 149.1, 145.9, 142.0, 138.2, 137.6, 137.5, 136.7, 134.9, 129.3, 128.8, 128.5, 128.2, 127.6, 127.5, 126.5, 126.4, 125.9, 125.0, 124.8, 124.1, 122.1, 121.9, 119.1, 119.0, 112.6, 112.3, 110.8, 105.5, 50.9, 43.4, 21.0 ppm. EI-HRMS: anal. calcd for $C_{33}H_{25}ClN_4O_2$: 544.1666, found: 544.1663.

5k: 1-Benzyl-5-chloro-3-(5-methoxy-1*H*-indol-3-yl)-3-(5-methyl-3-oxo-2-phenyl-2,3-dihydro-1*H*-pyrazol-4-yl)indolin-2-one. Isolated as a white solid, 88%, m.p.: 232–234 °C, ^{1}H NMR (400 MHz, DMSO-d_6): δ_H 10.93 (1H, s), 7.71 (1H, d, J = 7.9), 7.50 (1H, d, J = 8.0), 7.43 (2H, t, J = 8.0), 7.36 (3H, d, J = 2.2), 7.25 (H, dd, J = 24.1, 16.3), 7.13 (1H, d, J = 7.9), 6.83–6.74 (2H, m), 6.67 (1H, d, J = 2.3), 4.20 (2H, s), 3.81 (3H, s), 1.57 (3H, s) ppm. ^{13}C NMR (100 MHz, DMSO-d_6): δ_C 176.4, 153.3, 149.2, 142.0, 138.2, 137.5, 136.7, 134.9, 132.8, 129.4, 128.8, 128.6, 128.2, 127.5, 126.9, 126.4, 125.9, 125.1, 124.9, 124.8, 119.0, 112.8, 111.9, 111.7, 110.8, 105.3, 104.3, 55.7, 50.9, 43.4, 21.2 ppm. EI-HRMS: anal. calcd for $C_{34}H_{27}ClN_4O_3$: 574.1772, found: 574.1771.

Conflicts of interest

There are no conflicts to declare.

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