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REGIOSELECTIVE MULTICOMPONENT DOMINO REACTIONS PROVIDING RAPID AND EFFICIENT ROUTES TO FUSED ACRIDINES

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Abstract

Regioselective three-component reactions of aromatic aldehydes with indazol-5-amine and 2-hydroxy-1,4-naphthoquinone in HOAc under microwave irradiation have been developed. In this one-pot reaction, a series of new pyrazole-fused benzo[*h*]acridine derivatives with 1,2-diketone unit were synthesized with high chemical yields. The resulting pyrazole-fused acridines were employed to further react with aldehydes and ammonium acetate to give polycyclic oxazole-fused pyrazolo[3,4-*j*]acridines. The present green synthesis shows several advantages including operational simplicity and fast reaction rates, which makes it a useful and attractive process of library generation for drug discovery.

INTRODUCTION

The functional fused acridines, being the core structural unit in non-naturally and naturally occurring products, serve as “privileged structures” in many biologically active molecules and pharmaceutical substances;^{1,2} they have also been found in natural alkaloids, such as stelletamine,³ syclodercitin^{3,4} and plakinidines⁵ that show a broad range of biological activities. In addition, a variety of synthetic fused acridines exhibited biological activities including antitumor⁶ and antifungal.⁷ Therefore, this class of compounds has been the focus of pharmaceutical research,⁸ and has led to intensive interest in the synthesis of several drugs⁹. However, to the best of our knowledge, a direct and efficient synthesis of fused acridine derivatives incorporating both oxazole and pyrazole motifs have been not reported so far.

In modern organic synthesis, high-efficient synthetic strategies reflect the sum of enormous efforts aimed at atom-economic and environmental aspects and remarkable selective control of constructing natural products or natural-like structures.¹⁰ Multi-component domino reactions (MDRs) have been successfully applied to total synthesis of natural products,¹¹ becoming one of the key tools that allow the creation of several bonds in a one-pot manner and offer remarkable advantages of convergence, operational simplicity and facile automation.¹² These reactions not only can enable constructing complex structures in a single operation but also avoid tedious isolation and purification work-up. Among these methodologies, MDRs towards the formation of various heterocycles have been extensively studied.¹³ However, more efficient methodologies for the synthesis of azaheterocyclic products from readily available reactants remain to be extremely challenging.

Recently, we have developed a series of unique MDRs for the construction of multiple functional ring structures of chemical and pharmaceutical importance.¹⁴ As a result of our continuous effort on these domino processes, herein, we now found a new regioselective domino annulation providing an easy access to pyrazole-fused benzo[*h*]acridine derivatives. This reaction was achieved by reacting aromatic aldehydes, indazol-5-amine and 2-hydroxy-1,4-naphthoquinone under microwave irradiation (MW) in the absence of strong acids or metal catalysts/promoters (Scheme 1). The resulting pyrazole-fused acridines were employed to further react with aldehydes and ammonium acetate to give polycyclic heteroaromatics, oxazole-fused pyrazolo[3,4-*j*]acridines. The unique characteristic of the present domino reaction demonstrates that the formation of acridine *skeleton* and its bis-carbonylation were regioselectively achieved *via* metal-free [3+2+1] heterocyclization in a one-pot operation, and the resulting pyrazole-fused acridine possessing 1,2-diketone unit was a key building block, which can be converted into the oxazole-fused pyrazolo[3,4-*j*]acridines with high regioselectivity.

RESULTS AND DISCUSSION

It has been reported that when a mixture of an aromatic aldehyde, 2-hydroxy-1,4-naphthoquinone and naphthalen-2-amine was stirred in [bmim]BF₄ at room temperature, a cycloadduct dibenzo[*a,i*]acridine-1,6-diones **6** were produced in high yields¹⁵. After analyzing reaction mechanism, we reasoned that this reaction may have two different routes to the final products **6** or **4**: route i to the product **6**, and route ii to **4**. If the product **6** with 1,4-diketone unit was provided, the reaction of product **6** with aldehydes and ammonium acetate did not further undergo. On the contrary, the product **4** with 1,2-dicarbonyl groups if provided can react with aldehydes and ammonium acetate to generate fused aza-heterocycles. Based on the above analyses, we employed 4-bromobenzaldehyde **1a** to react with 2-hydroxy-1,4-naphthoquinone **2** and indazol-5-amine **3** in HOAc under microwave heating. After filtration, a red solid was obtained in 80% chemical yield. When the synthesized red solid was reacted with aldehydes and ammonium acetate, the yellow precipitate was observed. This product has been fully characterized by ¹H NMR, HRMS and IR spectral analysis. Furthermore, the structure of **5a** has been unambiguously determined by X-ray structural analysis as shown in Fig. 2. Thus, instead of compound **6**, the structure of red solid described above was pyrazole-fused acridines **4a** established on these experimental results.

We next began our investigation on three-component domino reaction of **1a**, **2** and **3**. When these components were mixed and subjected to microwave irradiation in acetic acid (HOAc) at 120 °C, an intermolecular pentacyclic product, pyrazole-fused acridines **4a**, was obtained in 80% yield. Subsequently, various solvents, such as water, EtOH, DMF, and trifluoroacetic acid (TFA), were thus employed as microwave irradiation media. Among these solvents, the first solvent (water) led to poor yields of product **4a** even at an enhanced temperature of 120 °C. Other three solvents, EtOH, DMF, and trifluoroacetic acid, resulted in product **4a** in 49%-63% isolated yields. Next, the influence of reaction temperature was also optimized, and the same reaction in HOAc was performed and repeated many times at different temperatures in a sealed vessel under microwave irradiation for 16 min. The yield of product **4a** was increased from 64% to 80% as the temperature varied from 100 to 120 °C. Further increase of reaction temperature failed to give a higher yield of desired product **4a** (entry 7). It was found that acetic acid can serve not only as a suitable media but also as an adequate Brønsted acid promoter for the present domino reactions.

With the above optimized conditions in hand, we then studied the substrate diversity of this HOAc promoted three-component domino reaction by using readily available starting materials. We were pleased to find that all the reactions proceeded efficiently and afforded the desired products in moderate to good yields. The results are presented in Table 2. The substituents on the phenyl ring of aldehydes did not hamper the reaction process. Reactions of bromo-, chloro-, fluoro-, nitro- or methyl-substituted aryl-aldehydes **1** with **2** and **3** all worked well to provide the desired products in good yields (Table 2, entries 1–7).

As an extension of the above study, we devised the synthesizing pyrazole-fused acridines possessing 1,2-diketone unit **4** to subject with **1** and ammonium acetate (excess) to investigate the possibility of this transformation under microwave irradiation. After several solvents were screened, DMF was found to be the most suitable solvent for this condensation to afford oxazole-fused pyrazolo[3,4-*j*]acridines **5** in excellent yields (78-89%) (Table 3) (Scheme 3). We found that reactants can not only be **4a-4e**, which possess electron-withdrawing substituents, such as bromo, chloro, and nitro groups at the *para* or *ortho*-position of the benzene ring, but also be **4g** having electron-donating substituent such as methyl group to give the corresponding diaryl-substituted oxazole-fused pyrazolo[3,4-*j*]acridines **5** in 80% yield. Besides aryl-aldehyde substrate, cyclopropyl, *s*-butyl, and *i*-butyl aldehydes were also found to be suitable for the present domino reaction to afford the expected 2-alkyl substituted oxazole-fused pyrazolo[3,4-*j*]acridines **5d-5g** in good yields. It is worth mentioning that the protocol provides a straightforward pathway to synthesize poly-functionalized fused acridines with high regioselectivity.

In addition to a high efficiency in the formation of multiple bonds, this reaction has the following advantages: (1) the reaction proceeds smoothly under very mild conditions without introducing strong acid, base or metal catalyst; (2) water is a sole by-product, which makes reaction process green; (3) the convenient work-up which only needs simple filtration since the products directly precipitate out after the reaction is finished¹⁶ and when its mixtures are diluted with cold water; and (4) the high regioselectivity in which the reactions generated fused acridine with 1,2-diketone unit that serve as important building blocks.

On the basis of all the above results, a possible mechanism has been proposed for the formations of fused acridines as shown in Scheme 4. The formation of **4** involves a ring closure cascade process that consists of initial condensation, intermolecular Michael addition (**A** to **B**), intramolecular nucleophilic cyclization (**B** to **C**), dehydration (**C** to **D**), and oxidation (**D** to **4**) (Scheme 4). The intermediate **B** favors the formation of intramolecular hydrogen bond between carbonyl group (position a) and *ortho*-hydroxyl group (position b), in which enolization of hydroxyl group was further enhanced. During this process, the carbonyl group (position c) would be easily attracted by the amino group ($-\text{NH}_2$) to give intermediate **C** which is then converted into the fused acridines *via* dehydration and oxidation steps.¹⁷ The synthesizing pyrazolo[3,4-*j*]acridines was further subjected with aldehydes and ammonium acetate to give final oxazole-fused pyrazolo[3,4-*j*]acridines **5** *via* [2+2+1] cyclization processes.

In summary, we have developed a new and convenient domino synthesis of polyfunctionalized fused acridines that can serve as versatile building blocks. The reaction showed high regioselectivity and broad scopes of substrates which can employ a wide range of common commercial starting materials. A new mechanism has been proposed to explain the reaction process and regioselectivity. The resulting pyrazolo[3,4-*j*]acridine products have been successfully converted into oxazole-fused pyrazolo[3,4-*j*]acridines by reacting with aldehydes and ammonium acetate under microwave irradiation. This reaction includes some important aspects like simple operation, easy accessibility of reactants and workup procedure, and metal-free catalysts. Further investigation on this method are currently under way and will be reported in due course.

EXPERIMENTAL

Microwave irradiation was carried out with Initiator 2.5 Microwave Synthesizers from Biotage Company, 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 $\text{DMSO}-d_6$ with chemical shift (δ) given in ppm relative to TMS as internal standard. HRMS (ESI) was determined by using microTOF-QII HRMS/MS instrument (BRUKER). X-Ray crystallographic analysis was performed with a Siemens SMART CCD and a Siemens P4 diffractometer

Synthesis of pyrazolo[3,4-*j*]acridine **4a** under microwave irradiation

In a 10-mL Initiator reaction vial, 2-hydroxy-1,4-naphthoquinone (**2**, 1.0 mmol), 4-bromobenzaldehyde (**1a**, 1.0 mmol), indazol-5-amine (**3**, 1.0 mmol) and HOAc (1.5 mL) were then successively added. Subsequently, the reaction vial was closed and then pre-stirred for 10 second. The mixture was irradiated (Time: 16 min, Temperature: 120 °C; Absorption Level: High; Fixed Hold Time) until TLC revealed that conversion of the starting material **1a** was complete. The reaction mixture was cooled to room temperature, and then the solid was obtained through filtration and washed with 2 mL 95% EtOH to give the almost pure product **4a**, which were further purified by recrystallization from 95% EtOH to afford the desired **4a**.

Synthesis of oxazole-fused pyrazolo[3,4-*j*]acridines **5** under microwave irradiation

In a 10-mL Initiator reaction vial, benzo[*h*]pyrazolo[4,3-*a*]acridine-11,12-dione (**4a**, 0.5 mmol), 4-bromobenzaldehyde (**1a**, 0.6 mmol), ammonium acetate (5 mmol) and DMF (1.5 mL) were then successively added. Subsequently, the reaction vial was closed and then pre-stirred for 10 second. The mixture was irradiated (Time: 20 min, Temperature: 120 °C; Absorption Level: High; Fixed Hold Time) until TLC revealed that conversion of the starting material **4a** was complete. The reaction mixture was cooled to room temperature and was poured into 20 ml water. The solid was obtained through filtration and washed with 2 mL 95% EtOH, to give the almost pure product **5a**, which was further purified by recrystallization from 95% EtOH to afford the desired **5a**.

13-(4-Bromophenyl)-3H-benzo[*h*]pyrazolo[4,3-*a*]acridine-11,12-dione (**4a**)

Mp: >300 °C;

IR (KBr, ν , cm^{-1}): 3302, 1668, 1593, 1535, 1484, 1377, 1276, 1202, 1169, 1012, 966, 932, 854;

^1H NMR (400 MHz, DMSO- d_6) (δ , ppm): 13.77 (s, 1H, NH), 8.92 (d, J = 7.6 Hz, 1H, ArH), 8.13 (d, J = 9.2 Hz, 1H, ArH), 8.09 (s, 1H, ArH), 8.05 (d, J = 7.6 Hz, 1H, ArH), 7.94 (t, J = 7.6 Hz, 1H, ArH), 7.88 (s, 1H, ArH), 7.86 (s, 1H, ArH), 7.68 (t, J = 7.6 Hz, 1H, ArH), 7.30 (s, 1H, ArH), 7.27 (s, 1H, ArH), 6.15 (s, 1H, ArH);

HRMS (ESI) m/z . calc. for $\text{C}_{24}\text{H}_{12}\text{BrN}_3\text{O}_2$: 476.0006 $[\text{M}+\text{Na}]^+$, found: 476.0008.

13-(4-Fluorophenyl)-3H-benzo[*h*]pyrazolo[4,3-*a*]acridine-11,12-dione (**4b**)

Mp: >300 °C;

IR (KBr, ν , cm^{-1}): 3387, 1672, 1606, 1594, 1505, 1457, 1378, 1255, 1109, 966, 934, 842;

^1H NMR (400 MHz, DMSO- d_6) (δ , ppm): 13.74 (s, 1H, NH), 8.91 (d, J = 8.0 Hz, 1H, ArH), 8.11 (d, J = 8.8 Hz, 1H, ArH), 8.04 (d, J = 8.8 Hz, 2H, ArH), 7.93 (t, J = 7.6 Hz, 1H, ArH), 7.67 (t, J = 7.2 Hz, 1H, ArH), 7.51 (t, J = 8.8 Hz, 2H, ArH), 7.37-7.33 (m, 2H, ArH), 6.12 (s, 1H, ArH); HRMS (ESI) m/z . calc. for $\text{C}_{24}\text{H}_{12}\text{FN}_3\text{O}_2$: 416.0806 $[\text{M}+\text{Na}]^+$, found: 416.0786.

13-(4-Chlorophenyl)-3H-benzo[*h*]pyrazolo[4,3-*a*]acridine-11,12-dione (**4c**)

Mp: >300 °C;

IR (KBr, ν , cm^{-1}): 3324, 1671, 1594, 1536, 1487, 1378, 1301, 1276, 1173, 1088, 1015, 933, 849;

^1H NMR (400 MHz, DMSO- d_6) (δ , ppm): 13.74 (s, 1H, NH), 8.91 (d, J = 8.0 Hz, 1H, ArH), 8.12 (d, J = 8.8 Hz, 1H, ArH), 8.04 (d, J = 8.8 Hz, 2H, ArH), 7.93 (t, J = 7.6 Hz, 1H, ArH), 7.73 (d, J = 8.8 Hz, 2H, ArH), 7.67 (t, J = 7.6 Hz, 1H, ArH), 7.35 (d, J = 8.4 Hz, 2H, ArH), 6.12 (s, 1H, ArH);

HRMS (ESI) m/z . calc. for $\text{C}_{24}\text{H}_{12}\text{ClN}_3\text{O}_2$: 432.0511 $[\text{M}+\text{Na}]^+$, found: 432.0514.

13-(2,4-Dichlorophenyl)-3H-benzo[*h*]pyrazolo[4,3-*a*]acridine-11,12-dione (4d)

Mp: >300 °C;

IR (KBr, ν , cm^{-1}): 3258, 1672, 1593, 1579, 1479, 1439, 1375, 1229, 1204, 1176, 1121, 968, 848;

^1H NMR (400 MHz, DMSO- d_6) (δ , ppm): 13.87 (s, 1H, NH), 8.92 (d, J = 8.0 Hz, 1H, ArH), 8.16 (d, J = 9.2 Hz, 1H, ArH), 8.11-8.05 (m, 2H, ArH), 8.01 (s, 1H, ArH), 7.94 (t, J = 7.6 Hz, 1H, ArH), 7.73 (d, J = 8.0 Hz, 1H, ArH), 7.69 (t, J = 7.6 Hz, 1H, ArH), 7.35 (d, J = 8.0 Hz, 1H, ArH), 6.28 (s, 1H, ArH); HRMS (ESI) m/z : calc. for $\text{C}_{24}\text{H}_{11}\text{Cl}_2\text{N}_3\text{O}_2$: 466.0121 [$\text{M} + \text{Na}$] $^+$, found: 466.0130.

13-(4-Nitrophenyl)-3H-benzo[*h*]pyrazolo[4,3-*a*]acridine-11,12-dione (4e)

Mp: >300 °C;

IR (KBr, ν , cm^{-1}): 3310, 1671, 1595, 1579, 1458, 1376, 1229, 1202, 1174, 1083, 935, 841;

^1H NMR (400 MHz, DMSO- d_6) (δ , ppm): 13.80 (s, 1H, NH), 8.92 (d, J = 7.6 Hz, 1H, ArH), 8.53 (d, J = 8.0 Hz, 2H, ArH), 8.14 (d, J = 9.2 Hz, 1H, ArH), 8.09 (s, 1H, ArH), 8.05 (d, J = 7.6 Hz, 1H, ArH), 7.93 (t, J = 7.6 Hz, 1H, ArH), 7.68 (t, J = 7.6 Hz, 1H, ArH), 7.63 (d, J = 8.4 Hz, 2H, ArH), 6.18 (s, 1H, ArH); HRMS (ESI) m/z : calc. for $\text{C}_{24}\text{H}_{12}\text{N}_4\text{O}_4$: 443.0751 [$\text{M} + \text{Na}$] $^+$, found: 443.0730.

13-Phenyl-3H-benzo[*h*]pyrazolo[4,3-*a*]acridine-11,12-dione (4f)

Mp: >300 °C;

IR (KBr, ν , cm^{-1}): 3432, 1671, 1614.

^1H NMR (400 MHz, DMSO- d_6) (δ , ppm): 13.69 (s, 1H, NH), 8.92 (d, J = 8.0 Hz, 1H, ArH), 8.11 (d, J = 9.2 Hz, 1H, ArH), 8.06 (s, 1H, ArH), 8.04 (s, 1H, ArH), 7.93 (t, J = 8.0 Hz, 1H, ArH), 7.68 (d, J = 7.6 Hz, 1H, ArH), 7.65 (s, 3H, ArH), 7.32-7.29 (m, 2H, ArH), 5.96 (s, 1H, ArH);

HRMS (ESI) m/z : calc. for $\text{C}_{24}\text{H}_{13}\text{N}_3\text{O}_2$: 398.0900 [$\text{M} + \text{Na}$] $^+$, found: 398.0878.

13-(*p*-Tolyl)-3H-benzo[*h*]pyrazolo[4,3-*a*]acridine-11,12-dione (4g)

Mp: >300 °C;

IR (KBr, ν , cm^{-1}): 3278, 1672, 1593, 1536, 1507, 1475, 1299, 1167, 1115, 1084, 934, 854;

^1H NMR (400 MHz, DMSO- d_6) (δ , ppm): 13.68 (s, 1H, NH), 8.90 (d, J = 8.0 Hz, 1H, ArH), 8.09 (d, J = 8.8 Hz, 1H, ArH), 8.03 (d, J = 7.2 Hz, 2H, ArH), 7.92 (t, J = 8.0 Hz, 1H, ArH), 7.66 (t, J = 7.6 Hz, 1H, ArH), 7.46 (d, J = 8.0 Hz, 2H, ArH), 7.18 (d, J = 7.6 Hz, 2H, ArH), 6.06 (s, 1H, ArH), 2.54 (s, 3H, CH_3); HRMS (ESI) m/z : calc. for $\text{C}_{25}\text{H}_{15}\text{N}_3\text{O}_2$: 412.1057 [$\text{M} + \text{Na}$] $^+$, found: 412.1047.

2,14-Bis(4-bromophenyl)-11H-benzo[c]oxazolo[5,4-a]pyrazolo[3,4-j]acridine (5a)

Mp: 261-262 °C;

IR (KBr, ν , cm^{-1}): 3416, 1618, 1598, 1478, 1385, 1319, 1261, 1011, 984, 831;

^1H NMR (400 MHz, $\text{DMSO}-d_6$) (δ , ppm): 13.78 (s, 1H, NH), 9.49 (d, $J = 7.6$ Hz, 1H, ArH), 8.42 (d, $J = 7.2$ Hz, 1H, ArH), 8.22 (d, $J = 9.2$ Hz, 1H, ArH), 8.11-8.07 (m, 3H, ArH), 7.90-7.84 (m, 2H, ArH), 7.71-7.65 (m, 4H, ArH), 7.53 (d, $J = 8.4$ Hz, 2H, ArH), 6.80 (s, 1H, ArH); HRMS (ESI) m/z : calc. for $\text{C}_{31}\text{H}_{16}\text{Br}_2\text{N}_4\text{O}$: 618.9764 $[\text{M}+\text{H}]^+$, found: 618.9768.

14-(4-Bromophenyl)-2-(*p*-tolyl)-11H-benzo[c]oxazolo[5,4-a]pyrazolo[3,4-j]acridine (5b)

Mp: >300 °C;

IR (KBr, ν , cm^{-1}): 3416, 1615, 1599, 1490, 1385, 1350, 1260, 1083, 984;

^1H NMR (400 MHz, $\text{DMSO}-d_6$) (δ , ppm): 13.71 (s, 1H, NH), 9.41 (d, $J = 8.0$ Hz, 1H, ArH), 8.34 (d, $J = 7.6$ Hz, 1H, ArH), 8.19-8.13 (m, 1H, ArH), 8.06-7.99 (m, 3H, ArH), 7.92-7.70 (m, 3H, ArH), 7.63 (d, $J = 8.0$ Hz, 1H, ArH), 7.47 (d, $J = 8.0$ Hz, 2H, ArH), 7.27 (t, $J = 8.0$ Hz, 2H, ArH), 6.75 (s, 1H, ArH), 2.37 (s, 3H, CH_3);

HRMS (ESI) m/z : calc. for $\text{C}_{32}\text{H}_{19}\text{BrN}_4\text{O}$: 555.0815 $[\text{M}+\text{H}]^+$, found: 555.0816.

14-(4-Bromophenyl)-2-(thiophen-2-yl)-11H-benzo[c]oxazolo[5,4-a]pyrazolo[3,4-j]acridine (5c)

Mp: >300 °C;

IR (KBr, ν , cm^{-1}): 3420, 1590, 1485, 1380, 1315, 1260, 1108, 984, 821;

^1H NMR (400 MHz, $\text{DMSO}-d_6$) (δ , ppm): 13.74 (s, 1H, NH), 9.45 (d, $J = 8.0$ Hz, 1H, ArH), 8.37 (d, $J = 7.6$ Hz, 1H, ArH), 8.18 (d, $J = 9.2$ Hz, 1H, ArH), 8.05 (d, $J = 8.4$ Hz, 2H, ArH), 7.94-7.86 (m, 2H, ArH), 7.84-7.77 (m, 2H, ArH), 7.64 (d, $J = 8.4$ Hz, 2H, ArH), 7.31-7.25 (m, 2H, ArH), 6.72 (s, 1H, ArH); HRMS (ESI) m/z : calc. for $\text{C}_{29}\text{H}_{15}\text{BrN}_4\text{OS}$: 547.0223 $[\text{M}+\text{H}]^+$, found: 547.0225.

14-(4-Bromophenyl)-2-cyclopropyl-11H-benzo[c]oxazolo[5,4-a]pyrazolo[3,4-j]acridine (5d)

Mp: >300 °C;

IR (KBr, ν , cm^{-1}): 3448, 1571, 1486, 1384, 1267, 1110, 1053, 985, 887;

^1H NMR (400 MHz, $\text{DMSO}-d_6$) (δ , ppm): 13.74 (s, 1H, NH), 9.50 (d, $J = 7.6$ Hz, 1H, ArH), 8.36 (d, $J = 7.6$ Hz, 1H, ArH), 8.27-8.20 (m, 1H, ArH), 8.08 (d, $J = 8.8$ Hz, 1H, ArH), 7.97 (d, $J = 8.4$ Hz, 2H, ArH), 7.92-7.81 (m, 2H, ArH), 7.54 (d, $J = 8.0$ Hz, 2H, ArH), 6.64 (s, 1H, ArH), 2.21-2.15 (m, 1H, CH), 1.10-1.08 (m, 2H, CH_2), 0.64-0.62 (m, 2H, CH_2);

HRMS (ESI) m/z : calc. for $\text{C}_{30}\text{H}_{23}\text{BrN}_4\text{O}$: 503.0503 $[\text{M}-\text{H}]^-$, found: 503.0508.

14-(4-Bromophenyl)-2-(sec-butyl)-11H-benzo[c]oxazolo[5,4-a]pyrazolo[3,4-j]acridine (5e)

Mp: >300 °C;

IR (KBr, ν , cm^{-1}): 3420, 1593, 1562, 1486, 1349, 1267, 1073, 928, 856;

^1H NMR (400 MHz, DMSO- d_6) (δ , ppm): 13.73 (s, 1H, NH), 9.45 (d, J = 7.6 Hz, 1H, ArH), 8.34 (d, J = 8.0 Hz, 1H, ArH), 8.16 (d, J = 9.2 Hz, 1H, ArH), 8.04 (d, J = 8.4 Hz, 1H, ArH), 7.95 (d, J = 8.4 Hz, 2H, ArH), 7.88-7.84 (m, 1H, ArH), 7.82-7.78 (m, 1H, ArH), 7.53 (d, J = 8.0 Hz, 2H, ArH), 6.63 (s, 1H, ArH), 2.94-2.89 (m, 1H, CH), 1.52 (t, J = 7.2 Hz, 2H, CH_2), 1.15 (d, J = 6.8 Hz, 3H, CH_3), 0.77 (t, J = 7.6 Hz, 3H, CH_3);

HRMS (ESI) m/z : calc. for $\text{C}_{29}\text{H}_{21}\text{BrN}_4\text{O}$: 519.0816 $[\text{M}-\text{H}]^-$, found: 519.0821.

14-(4-Bromophenyl)-2-isobutyl-11H-benzo[c]oxazolo[5,4-a]pyrazolo[3,4-j]acridine (5f)

Mp: >300 °C;

IR (KBr, ν , cm^{-1}): 3421, 1594, 1566, 1487, 1385, 1263, 1111, 1046, 929;

^1H NMR (400 MHz, DMSO- d_6) (δ , ppm): 13.72 (s, 1H, NH), 9.43 (d, J = 8.0 Hz, 1H, ArH), 8.32 (d, J = 7.2 Hz, 1H, ArH), 8.15 (d, J = 9.2 Hz, 1H, ArH), 8.02 (d, J = 8.8 Hz, 1H, ArH), 7.93 (d, J = 8.4 Hz, 2H, ArH), 7.87-7.77 (m, 2H, ArH), 7.52 (d, J = 8.0 Hz, 2H, ArH), 6.57 (s, 1H, ArH), 2.63 (d, J = 7.2 Hz, 2H, CH_2), 1.87-1.80 (m, 1H, CH), 0.84 (t, J = 6.4 Hz, 6H, CH_3);

HRMS (ESI) m/z : calc. for $\text{C}_{29}\text{H}_{21}\text{BrN}_4\text{O}$: 519.0816 $[\text{M}-\text{H}]^-$, found: 519.0842.

14-(4-Chlorophenyl)-2-cyclohexyl-11H-benzo[c]oxazolo[5,4-a]pyrazolo[3,4-j]acridine (5g)

Mp: >300 °C;

IR (KBr, ν , cm^{-1}): 3419, 1598, 1567, 1487, 1384, 1262, 1088, 1045, 928, 847;

^1H NMR (400 MHz, DMSO- d_6) (δ , ppm): 13.74 (s, 1H, NH), 9.45 (d, J = 8.4 Hz, 1H, ArH), 8.33 (d, J = 7.6 Hz, 1H, ArH), 8.19 (d, J = 9.2 Hz, 1H, ArH), 8.06 (d, J = 9.2 Hz, 1H, ArH), 7.88-7.78 (m, 4H, ArH), 7.61 (d, J = 8.4 Hz, 2H, ArH), 6.67 (s, 1H, ArH), 2.84 (s, 1H, CH), 1.81 (d, J = 11.2 Hz, 2H, CH_2), 1.65 (d, J = 6.8 Hz, 3H, CH_2), 1.36-1.25 (m, 5H, CH_2);

HRMS (ESI) m/z : calc. for $\text{C}_{31}\text{H}_{23}\text{ClN}_4\text{O}$: 503.1634 $[\text{M}+\text{H}]^+$, found: 503.1635.

14-(2,4-Dichlorophenyl)-2-(4-methoxyphenyl)-11H-benzo[c]oxazolo[5,4-a]pyrazolo[3,4-j]acridine (5h)

Mp: >300 °C;

IR (KBr, ν , cm^{-1}): 3415, 1617, 1570, 1490, 1373, 1315, 1260, 1161, 1087, 985, 855;

^1H NMR (400 MHz, DMSO- d_6) (δ , ppm): 13.87 (s, 1H, NH), 9.55 (d, J = 8.4 Hz, 1H, ArH), 8.50 (d, J = 7.6 Hz, 1H, ArH), 8.29-8.26 (m, 2H, ArH), 8.15 (d, J = 9.2 Hz, 1H, ArH), 7.97-7.89 (m, 3H, ArH), 7.84 (d, J = 8.0 Hz, 1H, ArH), 7.66 (d, J = 9.2 Hz, 2H, ArH), 7.09 (d, J = 8.8 Hz, 2H, ArH), 6.87 (s, 1H, ArH), 3.89 (s, 3H, OCH_3);

HRMS (ESI) m/z : calc. for $C_{32}H_{18}Cl_2N_4O_2$: 561.0880 $[M+H]^+$, found: 561.0886.

14-(4-Nitrophenyl)-2-(*p*-tolyl)-11*H*-benzo[*c*]oxazolo[5,4-*a*]pyrazolo[3,4-*j*]acridine (5i)

Mp: >300 °C;

IR (KBr, ν , cm^{-1}): 3415, 1613, 1601, 1516, 1493, 1384, 1262, 1181, 1044, 933, 843;

1H NMR (400 MHz, DMSO- d_6) (δ , ppm): 13.80 (s, 1H, NH), 9.52 (d, J = 8.0 Hz, 1H, ArH), 8.71 (d, J = 8.8 Hz, 2H, ArH), 8.45 (d, J = 7.2 Hz, 1H, ArH), 8.25 (d, J = 9.2 Hz, 1H, ArH), 8.11 (d, J = 8.8 Hz, 1H, ArH), 8.04 (d, J = 8.4 Hz, 2H, ArH), 7.91-7.86 (m, 2H, ArH), 7.44 (d, J = 8.0 Hz, 2H, ArH), 7.23 (d, J = 8.0 Hz, 2H, ArH), 6.73 (s, 1H, ArH), 2.37 (s, 3H, CH₃);

HRMS (ESI) m/z : calc. for $C_{32}H_{19}N_5O_3$: 522.1561 $[M+H]^+$, found: 522.1564.

2-(4-Methoxyphenyl)-14-phenyl-11*H*-benzo[*c*]oxazolo[5,4-*a*]pyrazolo[3,4-*j*]acridine (5j)

Mp: >300 °C;

IR (KBr, ν , cm^{-1}): 3415, 1616, 1560, 1494, 1385, 1307, 1255, 1179, 1095, 985, 829;

1H NMR (400 MHz, DMSO- d_6) (δ , ppm): 13.69 (s, 1H, NH), 9.49 (d, J = 7.6 Hz, 1H, ArH), 8.41 (d, J = 7.2 Hz, 1H, ArH), 8.20 (d, J = 9.2 Hz, 1H, ArH), 8.05 (d, J = 9.2 Hz, 1H, ArH), 7.91-7.82 (m, 5H, ArH), 7.66 (d, J = 7.2 Hz, 2H, ArH), 7.55 (d, J = 8.8 Hz, 2H, ArH), 7.03 (d, J = 8.8 Hz, 2H, ArH), 6.51 (s, 1H, ArH), 3.85 (s, 3H, OCH₃);

HRMS (ESI) m/z : calc. for $C_{32}H_{20}N_4O_2$: 493.1660 $[M+H]^+$, found: 493.1646.

2-(4-Methoxyphenyl)-14-(*p*-tolyl)-11*H*-benzo[*c*]oxazolo[5,4-*a*]pyrazolo[3,4-*j*]acridine (5k)

Mp: 208-210 °C;

IR (KBr, ν , cm^{-1}): 3435, 1611, 1553, 1496, 1384, 1256, 1171, 1087, 985, 837;

1H NMR (400 MHz, DMSO- d_6) (δ , ppm): 13.67 (s, 1H, NH), 9.49 (d, J = 8.0 Hz, 1H, ArH), 8.42 (d, J = 7.6 Hz, 1H, ArH), 8.20 (d, J = 9.2 Hz, 1H, ArH), 8.05 (d, J = 8.8 Hz, 1H, ArH), 7.89-7.78 (m, 2H, ArH), 7.66 (d, J = 7.6 Hz, 2H, ArH), 7.57-7.51 (m, 4H, ArH), 7.03 (d, J = 8.8 Hz, 2H, ArH), 6.69 (s, 1H, ArH), 3.86 (s, 3H, OCH₃), 2.72 (s, 3H, CH₃);

HRMS (ESI) m/z : calc. for $C_{33}H_{22}N_4O_2$: 507.1816 $[M+H]^+$, found: 507.1816.

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18. Crystal data for **6a**: $C_{32.50}H_{19.50}Br_2N_5O_2$, Monoclinic, space group $P2(1)/c$, $a = 13.2717(14) \text{ \AA}$, $b = 9.4389(9) \text{ \AA}$, $c = 26.075(3) \text{ \AA}$, $\alpha = \gamma = 90^\circ$, $\beta = 111.7760(10)^\circ$, $V = 3033.3(5) \text{ \AA}^3$, $Mr = 671.85$, $Z = 4$, $D_c = 1.471 \text{ Mg/m}^3$, $\lambda = 0.71073 \text{ \AA}$, $\mu(\text{Mo K}\alpha) = 2.710 \text{ mm}^{-1}$, $R(000) = 1342$, $R = 0.1088$, $wR_2 = 0.2242$, largest diff. Peak and hole: 1.589 and -0.513 $e/\text{\AA}^3$.

Figure 1.
Several representative natural products

Scheme 1.
Synthesis of polysubstituted azaheterocyclic products

Scheme 2. Regioselective synthesis of azaheterocyclic product **6** or **4**

Scheme 3.

Domino synthesis of oxazole-fused pyrazolo[3,4-*j*]acridines **5**

Scheme 4.

Possible mechanism for the formation of fused acridines **4** and **5**

Table 1Conditions optimization for the synthesis of **4a** under MW

Entry	Solvent	T / °C	Time / min	Yield (%)
1	Water	120	16	25
2	EtOH	120	16	52
3	DMF	120	16	63
4	CF ₃ COOH	120	16	49
5	HOAc	120	16	80
6	HOAc	100	16	64
7	HOAc	130	16	79

Table 2The domino synthesis of pyrazole-fused acridines **4**

Entry	Product	R	Time (min)	Yield (%)
1	4a	4-BrC ₆ H ₄ (1a)	16	80
2	4b	4-FC ₆ H ₄ (1b)	16	85
3	4c	4-ClC ₆ H ₄ (1c)	15	83
4	4d	2,4-Cl ₂ C ₆ H ₃ (1d)	14	82
5	4e	4-NO ₂ C ₆ H ₄ (1e)	15	87
6	4f	C ₆ H ₅ (1f)	15	80
7	4g	4-MeC ₆ H ₄ (1g)	16	79

Table 3The domino synthesis of oxazole-fused pyrazolo[3,4-*j*]acridines **5**

Entry	5	R	4	R'	Time (min)	Yield (%)
1	5a	4-BrC ₆ H ₄ (1a)	4a	4-BrC ₆ H ₄ (1a)	26	89
2	5b	4-BrC ₆ H ₄ (1a)	4a	4-MeC ₆ H ₄ (1g)	24	80
3	5c	4-BrC ₆ H ₄ (1a)	4a	2-Thienyl (1h)	23	82
4	5d	4-BrC ₆ H ₄ (1a)	4a	Cyclopropyl (1i)	30	85
5	5e	4-BrC ₆ H ₄ (1a)	4a	<i>s</i> -Butyl (1j)	32	83
6	5f	4-BrC ₆ H ₄ (1a)	4a	<i>i</i> -Butyl (1k)	34	78
7	5g	4-ClC ₆ H ₄ (1c)	4c	Cyclohexyl (1i)	30	79
8	5h	2,4-Cl ₂ C ₆ H ₃ (1d)	4d	4-MeOC ₆ H ₄ (1l)	28	82
9	5i	4-NO ₂ C ₆ H ₄ (1e)	4e	4-MeC ₆ H ₄ (1g)	24	87
10	5j	C ₆ H ₅ (1f)	4f	4-MeOC ₆ H ₄ (1l)	26	88
11	5k	4-MeC ₆ H ₄ (1g)	4g	4-MeOC ₆ H ₄ (1l)	28	80