RSC Advances

PAPER

View Article Online
View Journal | View Issue

Cite this: *RSC Adv.*, 2023, **13**, 16377

Synthesis of structural analogues of Reversan by ester aminolysis: an access to pyrazolo[1,5-*a*] pyrimidines from chalcones†

Andres Arias-Gómez,[a] Mario A. Macías[b] and Jaime Portilla *[a]

Received 17th April 2023
Accepted 17th May 2023

DOI: 10.1039/d3ra02553e

rsc.li/rsc-advances

Reversan, a multidrug resistance-associated protein (MRP1) inhibitor described more than a decade ago, is a commercial drug (CAS: 313397-13-6) that has a high price and is six to eight times more potent than known drug transporter inhibitors. However, to date, a complete route for synthesizing pyrazolo[1,5-*a*] pyrimidine-based Reversan is yet to be published. Herein, the silica gel-mediated synthesis of Reversan and a novel family of its structural analogues (amides) *via* the microwave-assisted amidation reaction of 3-carboethoxy-5,7-diphenylpyrazolo[1,5-*a*]pyrimidine (ester) with primary amines is reported. Moreover, a set of this ester-type precursor was obtained using the NaF/alumina-mediated reaction of 5-amino-3-carboethoxy-1*H*-pyrazole with chalcones, implying a final removal of H_2 using $Na_2S_2O_8$. Both esters and amides were obtained in high yields using heterogeneous catalyst and solvent-free, highly efficient, and scalable synthetic protocols.

Introduction

Intrinsic or acquired multidrug resistance is one of the leading causes of treatment failure in human malignancies; thus, finding new ways to solve this problem has attracted special attention from chemists, biologists, pharmacists, and related professionals. Molecular-level investigations of cancer multidrug resistance have revealed that two ATP-binding cassette transporters cause resistance in tumor cells: *P*-glycoprotein and the multidrug resistance-associated protein (MRP1).[1,2] The overexpression of MRP1 in almost all tumor types (*e.g.*, lung, melanoma, sarcoma, neuroblastoma, head, and breast) lowers the intracellular drug concentration.[3–5] About this, Burkhart *et al.*[6] reported a way to overcome MRP1 activity using Reversan, a pirazolo[1,5-*a*]pyrimidine (PP) derivative having an *N*-(3-morpholinopropyl)carboxamide group at position 3 and two phenyl rings at positions 5 and 7, which is commercially available but has a high price (Fig. 1a).

Reversan is six to eight times more potent in inhibiting MRP1 than known drug carrier inhibitors (*i.e.*, verapamil, difloxacin, probenecid, and PAK104P).[6] Despite the high biological effects described over a decade ago, a synthetic route for Reversan or its structural analogues is yet to be reported. Hence, obtaining this family of pyrazolo[1,5-*a*]pyrimidines (PPs) is challenging. In this line, our group has focused on obtaining diverse functionalized PPs,[7,8] mostly investigating their photophysical properties as a promising approach,[9,10] adding to recurring biological applications of these compounds.[10–13] PP ring access is usually achieved by constructing the pyrimidine moiety *via* the cyclocondensation reaction of *NH*-5-aminopyrazoles with 1,3-bis(electrophiles) such as ynones, β-dicarbonyls, β-enamionones, and β-ketonitriles, which permit the involved unsaturation in products (Fig. 1b).[10–13] However, although chalcones (enones) yield 5,7-diaryl derivatives with greater molecular diversity than similar substrates (*e.g.*, β-diketones such as diaroylmethane), enones are rarely used because mixtures of products with the dihydro derivative (or perhaps some regioisomer) are obtained; more rigorous conditions or further steps are required to obtain the aromatic ring (Scheme 1a).[8,14–18]

The poor aromatic character of the pyrimidine ring inside the PP core possibly is an insignificant driving force that favors

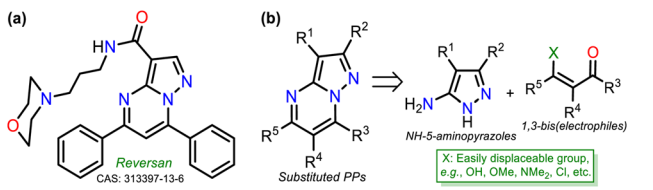
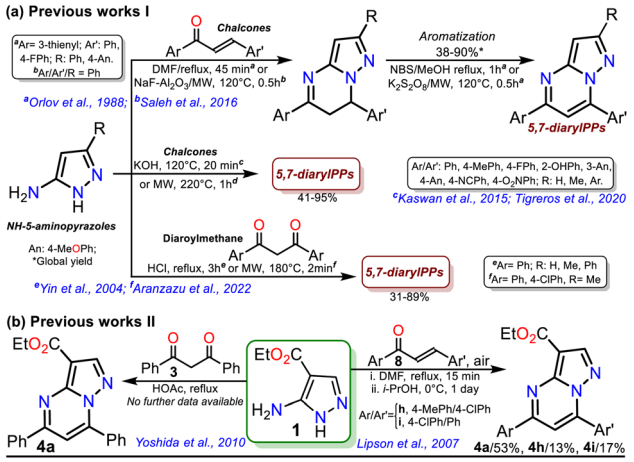


Fig. 1 (a) Molecular structure of Reversan and (b) retrosynthetic analysis of PPs.

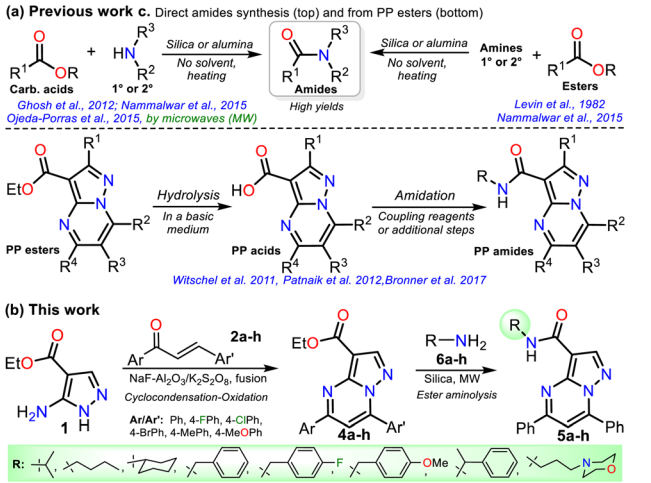
[a]*Department of Chemistry, Bioorganic Compounds Research Group, Universidad de Los Andes, Carrera 1 No. 18A-10, Bogotá 111711, Colombia. E-mail: jportill@uniandes.edu.co*

[b]*Department of Chemistry, Crystallography and Chemistry of Materials, Universidad de Los Andes, Carrera 1 No. 18A-10, Bogotá, Colombia*

† Electronic supplementary information (ESI) available: spectra (NMR and HRMS), and crystallographic details. CCDC **4a** 2249102, **4g** 2249098, **5a** 2249101, **5d** 2249099, and **5h** 2249100. For ESI and crystallographic data in CIF or other electronic format see DOI: https://doi.org/10.1039/d3ra02553e



Scheme 1 Synthesis of 5,7-diaryl PPs using (a) 5-aminopyrazoles or (b) amimoester **1**.



Scheme 2 (a) Synthesis of amides by solid-supported catalysts and using PP esters. (b) Proposal for synthesizing reversan (**5h**) and its structural analogues.

π-conjugation in products.[10–13] As a result, there are even rarer examples for synthesizing PPs from chalcones **2** and *NH*-5-aminopyrazoles bearing an electron-withdrawing group (EWG), such as ethyl-5-amino-1*H*-pyrazole-4-carboxylate (**1**), which is a crucial substrate in Reversan synthesis since they are poorly reactive 1,3-bis-(nucleophiles).[19] To date, only four articles where precursor **1** gives 5,7-diarylpyrazolo[1,5-*a*]pyrimidines **4** have been published; in two of these, an acid-mediated tri-component reaction with arylaldehydes and arylacetylene was carried out,[20,21] while in the other two, chalcones **2** (ref. 22) or dibenzoylmethane (**3**)[23] were used as substrates (Scheme 1b). However, in these last two works, the results and characterization data are unsatisfactory.

On the other hand, ester aminolysis is possibly the least common method for forming amides, one of the most appreciated functional groups in biologically relevant compounds.[24–28] The low recurrence of direct ester amidation is possibly because the reactions require high temperatures. Under this condition, substrates are susceptible to decomposition or easy evaporation, especially liquid ones, leading to a loss of mass efficiency or low reaction yields.[24–26] The usual methods for preparing amides involve reacting carboxylic acids or acylating agents (*i.e.*, acid anhydrides, acid chlorides, and acids with additives) with amines. However, most of these methods require excess amine, catalysts, coupling reagents, solvents excess, or high temperatures with prolonged reaction times, leading to protocols with a poor atom economy, generating toxic wastes, and spending energy.[24–29] Thus, the solvent-free direct amidation reaction of carboxylic acids or esters by heterogeneous catalysis using silica or alumina is a suitable method, though little-used, to efficiently access amides due to the value and easy disposal of these solids (Scheme 2a).[29–33]

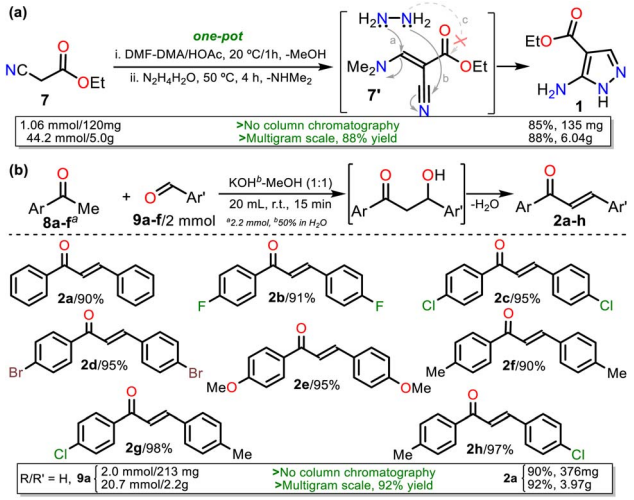
Due to the biological importance of pyrazolo[1,5-*a*] pyrimidines[10–13] and the amide functional group,[24–28] there are several examples of synthesis of this *N*-heterocycle substituted at position 3 with the carboxamide group. However, when the respective ester is used as a starting reagent, the synthesis proceeds by hydrolysis and subsequent amidation under conditions that imply coupling agents, further reaction steps, and poor yields (Scheme 2b).[34–36] Pondering these findings and the relevance of reversan, we envisioned that this amide and a novel family of its structural analogues (PPs **5a–h**) could be synthesized through the direct amidation reaction of ethyl-5,7-diphenylpyrazolo[1,5-*a*]pyrimidine-3-carboxylate (**4a**) with primary alkylamines **6a–h**. Likewise, due to the moderate use of chalcones in PPs syntheses and our interest in accessing this type of heterocycle by eco-compatible methods from easily accessible reagents,[7–10,17] we also proposed obtaining the 5,7-diarylsubstituted esters **4a–h** by the reaction of **1** with chalcones **2a–h** (Scheme 2c). Ultimately, we look for the synthesis of **4a–h** and **5a–h** through green approaches.

Results and discussion

Synthesis of pyrazolo[1,5-*a*]pyridimidines 4a–h

We started our investigation by preparing precursors such as ethyl-5-amino-1*H*-pyrazole-4-carboxylate (**1**) and chalcones **2a–h** *via* known protocols that resulted in high yields. Aminoester **1** was obtained as white crystals after its recrystallization from ethanol using a one-pot approach starting with the reaction of ethyl cyanoacetate (**7**) and DMF-DMA to access the 1,3-bis(electrophilic) intermediate **7′**; then, upon adding hydrazine monohydrate (HM), the cyclocondensation reaction of this with the β-enaminonitrile moiety of **7′** (route a + b), instead of its less reactive β-enaminoester fragment (a + c), occurs to access the desired product in a regioselective manner (Scheme 3a).[19,37] Chalcones **2a–h** were prepared by the Claisen–Schmidt condensation reaction between acetophenone **8a–f** and arylaldehydes **9a–f** in methanol/water (1 : 1 v/v), a basic medium, short reaction times, and simple purification by recrystallization (Scheme 3b).[38]

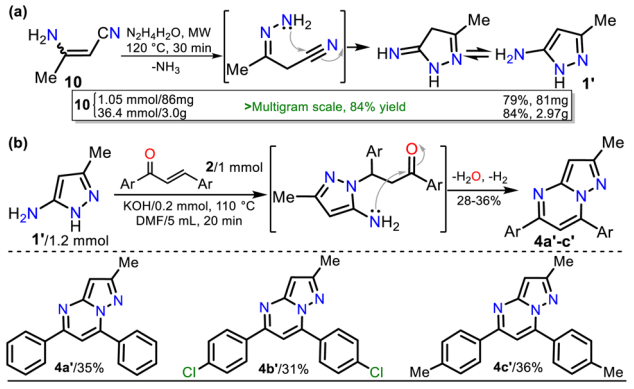
On the other hand, 3-methyl-1*H*-pyrazol-5-amine (**1′**)[39] was prepared to examine the best protocol reported[16] to access PPs starting from chalcones (see Scheme 1a above). Amine **1′** was



Scheme 3 Synthesis of (a) aminoester **1** and (b) chalcones **2a–h**.

synthesized from 3-aminocrotononitrile (**10**) and HM (1.5 equiv.) by a modified method at 120 °C for 30 min under microwave; amine **1′** was purified by flash chromatography (Scheme 4a). Subsequently, we carried out the syntheses of **1**, **2a**, and **1′** on a scale of about 6, 4, and 3 g, respectively, as they are strategic substrates in our laboratory (Schemes 3 and 4a, data in rectangles). Notably, precursors **1** and **2a** were crucial for this work and obtained without chromatographic purification. In addition, increasing the scale also resulted in a slight increase in yields of **1** (from 85 to 88%), **2a** (from 90 to 92%), and **1′** (from 79 to 84%).

With the required precursors in hand, we envisaged that the reaction of **1** and **2a–h** could give 3-carboethoxypyrazolo[1,5-*a*] pyrimidines **4a–h** by the standard route, related to previous works (see Schemes 1 and 2b). In this way, we reproduce the synthesis of **4a′** by Kaswan *et al.*,[16] where they obtained the product in 82% yield from the amine **1′**, chalcone (**2a**) and KOH as a catalyst in DMF; however, we obtained moderate yield despite the experimental variants used (*i.e.*, time and MW heating). Then, we obtained two other PPs (**4b′–c′**), but the results did not improve; thus, although products can be



Scheme 4 Synthesis of (a) 3-methyl-1*H*-pyrazol-5-amine (**1′**) and (b) PPs **4a′–b′**.

obtained as reported, this protocol must be revised (Scheme 4b). These results made us question the reactivity of chalcones toward aminoester **1**, which is even less nucleophilic than amine **1′**.

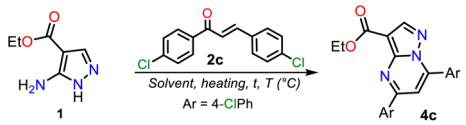
In general, obtaining the PP esters **4a–h** using chalcones **2a–g** and aminoester **1** is a great challenge due to the reactivity of substrates, the easy access to **2a–g** from cheap reagents, and even more due to the absence of a standard method for this synthesis. Thus, we started the study by exploring the reaction of **1** with an equimolar amount of **2c** (Ar = 4-ClPhl) to optimize this reaction. We selected **2c** due to its high electrophilic character, and the chlorophenyl group generally allows us simple purification processes and follow-up by ^{1}H NMR. By thin-layer chromatography (TLC), we noted that reactions did not proceed or occur with poor conversion under similar conditions to those used in our laboratory for similar reactions, *i.e.*, without or with polar solvent under microwave, allowing us to carry out several tests quickly.[40] Similar results were evidenced under heating to reflux and using non-nucleophilic bases. Decomposition products were obtained by heating the reaction above 180 °C (Table 1, entries 1 to 4).

Due to the initial adverse results, we used heterogeneous catalysts such as silica gel, alumina, or NaF/alumina as in the work of Saleh *et al.*[14] where potassium persulfate ($K_2S_2O_8$) was added to favor the oxidation step (Scheme 1a above). The catalytic effect of these solids is based on their diverse acidity (silica < Al_2O_3 < NaF–Al_2O_3)[41,42] or maybe the NaF–Al_2O_3 basicity to *NH*-azoles for the fluoride anion.[43] Ester **4c** was obtained in poor yields using these solid catalysts (Table 1, entries 5 to 7), but with NaF–Al_2O_3, the yields can be increased using a higher F^- concentration in the solid or varying the mixture amount;[44] however, the reaction time is crucial for the process (Table 1, entries 7 to 11). These results established that a yield greater than 60% was achieved with catalytic amounts of NaF–Al_2O_3 (Table 1, entry 11). The best yield was found when the reaction was heated in fusion using a sand bath at 180 °C for 10 min. In the absence of $K_2S_2O_8$ under the optimized conditions, the yield was reduced to 43%, confirming the importance of this oxidizing agent (Table 1, entry 12 *vs.* 13).

Next, the reaction scope using various chalcones and the optimized conditions was examined. The reaction of an equimolar mixture of **1** with **2a–h** (0.5 mmol) in the presence of NaF–Al_2O_3 (3 : 5 w/w, 25 mg) under heating at 180 °C for 10 min and then adding $K_2S_2O_8$ (1 equiv.) to heat for another 5 min at 100 °C afforded the novel family of ethyl-5,7-diarylpyrazolo[1,5-*a*] pyrimidine-3-carboxylates **4a–h** in high yields. Notably, substrates **2a–f** have the same aryl group, which differs in **2g–h**; this feature allows us to better establish the reaction regioselectivity in the initial step to form PPs **4a–h** (Scheme 5).

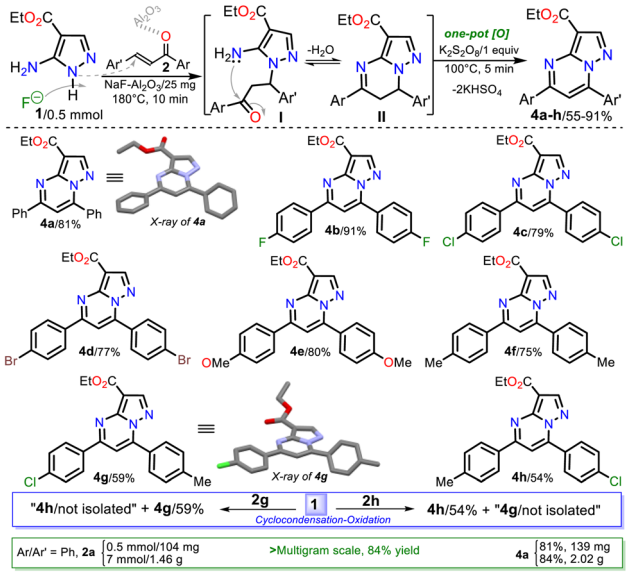
Almost no loss of efficiency was observed in the synthesis of **4a–h** with the chalcones tested, evidencing that the electronic demands of the substituents had little influence on the reactivity beyond the possible decomposition or evaporation of reagents under the established reaction conditions. However, the lowest yields were obtained using chalcones **2g–h**, possibly due to the formation of **4h** (using **2g**) and **4g** (using **2h**), which are regioisomers of esters **4g** and **4h**, respectively (Scheme 5,

Table 1 Optimization of the synthesis of the pyrazolo[1,5-*a*]pyrimidine **4c**[a]



Entry	Solvent and/or additive	*T* (°C)	Time *t*	Yield (%)
1	S-F, DMF, HOAc, or EtOH	120–200[b]	60 min	Traces
2	DMF, HOAc, or EtOH	Reflux	24 h	Traces
3	S-F, DMF/Cs_2CO_3, or Et_3N (1 equiv.)	180[b]	60 min	NR
4	DMF, Cs_2CO_3, or Et_3N (1 equiv.)	Reflux	24 h	Traces
5	Silica gel (100 mg)	130[b]	15 min × 3	12
6	Al_2O_3 (100 mg)	200[b]	15 min × 4	6
7	NaF–Al_2O_3 (0.2 : 1, 100 mg)[c]	180[b]	15 min × 4	14
8	NaF–Al_2O_3 (0.4 : 1, 100 mg)[c]	180[b]	15 min × 4	20
9	NaF–Al_2O_3 (0.6 : 1, 100 mg)[c]	180[b]	15 min × 4	40
10	NaF–Al_2O_3 (0.6 : 1, 50 mg)[c]	180[b]	15 min × 2	24
11	NaF–Al_2O_3 (0.6 : 1, 10 mg)[c]	180[b]	15 min × 4	62
12	NaF–Al_2O_3 (0.6 : 1, 10 mg)[c]	180[d]	10 min	81
13	NaF–Al_2O_3 (0.6 : 1, 10 mg)	180[d]	10 min	43

[a] Reactions conditions: **1** and **2c** (0.2 mmol) in 1.0 mL solvent under heating in a mantle: NR = no reaction. [b] Run in a 10 mL sealed tube under MW in 0.5 mL solvent or solvent-free (S-F) conditions. [c] $K_2S_2O_8$ (0.2 mmol) is added, and the reaction is heated for another 5 min at 100 °C. [d] A tubular reaction vessel was charged with the mixture and heated by a sand bath.



Scheme 5 Synthesis of PPs **4a–h**. A plausible formation way of **4a–h** is shown.

blue rectangle); in any case, the high regioselectivity of reactions was demonstrated. Due to ester **4a** being the key precursor for synthesizing the final products in this work (*i.e.*, Reversan and analogue amides), we carried out its synthesis on a scale of 2 g (Schemes 5, green rectangle). In this case, increasing the scale also resulted in a slight increase in the yields of **4a** (from 81 to 84%).

Although there are reports for preparing PPs *via* the reaction of *NH*-5-aminopyrazoles with chalcones,[14–17] a reasonable reaction route to yield products **4a–h** under the optimized conditions in this work was established (Scheme 5 at the top). The reaction begins with an *aza*-Michael addition of the pyrrolic-like nitrogen atom in **1** (N1) to the Cβ of **2a–f**, leading to intermediate I through a typical and dominant soft–soft interaction (Fig. 2).[11,45,46] This attack is probably favored by fluoride ions (F^-) in the catalyst, having a verified ability to remove the hydrogen atom from *NH*-azoles;[43] likewise, the enone increases its electrophilicity when the carbonyl group interacts with alumina. Then, the cyclcondensation of **I** with the loss of a water molecule occurs to afford the dihydro derivative II (NH_2/hard → C=O/hard), which is oxidized to the product **4a–h** with $K_2S_2O_8$ (1 equiv.) that favors the removal of hydrogen by converting to potassium bisulfate ($KHSO_4$).[14]

Gratifyingly, structures of compounds **4a** and **4g** were solved by single-crystal X-ray diffraction analysis (see ESI†† for details). These results allowed us to verify the reaction course since substrate **2g**, which leads to **4g**, has two different aryl groups. It was impossible to establish the regioselectivity of the cyclocondensation reaction only using NMR analysis such as NOESY or HMBC experiments (Fig. 2).

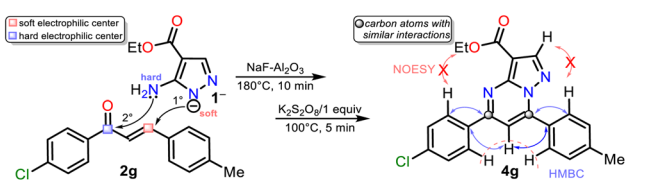


Fig. 2 Synthesis of ethyl PPs **4a–h**. A plausible formation way of **4a–h** is shown.

It is important to mention what was cited in the introduction section: only four articles on obtaining 5,7-diarylpyrazolo[1,5-*a*] pyrimidines **4** starting from aminoester **1** have been published.[20–23] In fact, only one of these works is comparable with synthesizing the eight PPs **4a–h** because chalcones were used as substrates,[22] and only compounds **4a** and **4f** have been reported in the literature. However, the method developed in this research presented better results than the cited works regarding process efficiency, synthetic versatility, and substrate scope (*e.g.*, chalcones or enones are easily accessible both synthetically and cheaply) and/or yields (see Scheme 1 above).[20–23]

Synthesis of Reversan and analogues 5a–h

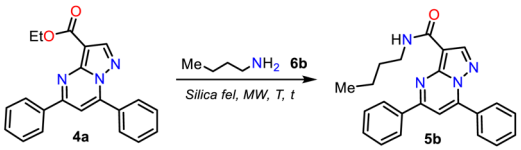
Once PPs **4a–h** were obtained, we selected compound **4a** to develop a simple and green method to generate Reversan and its structural analogues **5a–h** by the direct amidation reaction of this ester with primary alkylamines **6a–h**. In the amides synthesis on PPs, the respective carboxylic acid is used as a precursor; however, due to the possibility of the direct amidation of ester **4a**, we tried to synthesize the *N*-butycarboxamide **5b** with *n*-butylamine (**2b**) as a model reagent that allows us to optimize the conditions for this transformation, saving the hydrolysis step, although this reaction type is minorly used. Thus, considering our interest in MW-mediated reactions[40] and the results of the NaF/alumina-catalyzed synthesis of **4a–g**, we decided to start the study using similar conditions to those described by Ojeda-Porras *et al.*;[33] they achieved the amidation of carboxylic acids with amines by irradiating an equimolar mixture (1.5 mmol) of reagents supported on silica gel (1.0 g) with MW for 4 cycles of 20 min at 130 °C (see Scheme 2a above). However, our results were not encouraging even after increasing the time and temperature (Table 2, entries 1 to 3).

Because **6b** is a volatile amine, we decided to double its proportion (from 0.15 to 0.30 mmol), wanting this would favor the reaction; however, it was only possible to observe the forming **5b** in moderate yield after 1 hour of reaction at 180 °C (Table 2, entries 4 to 7). Next, we tripled the proportion of **6b** (0.45 mmol), allowing us to form **5b** in good yields, but the reaction is not better at less than 180 °C or more than 30 min (Table 2, entries 8 to 10).

Consequently, the optimal reaction conditions to obtain **5b** use ~3 equivalents of starting amine **6b** and 0.1 g silica gel at 180 °C for 30 min under microwave irradiation (Table 2, entry 9); we employed these conditions to examine the amidation reaction scope with various commercial primary alkylamines **6a–h**. Fortunately, the MRP1 inhibitor, Reversan (**5h**), was obtained by the reaction of **4h** with 3-morpholinopropanamine (**6h**); likewise, using alkylamines **6a–g**, the Reversan structural analogues **5a–g** were obtained, and all the synthesized amides were obtained in high yields. Moreover, crystals of suitable size and quality for single-crystal X-ray diffraction analysis of products **5a** (*N*-iPr), **5d** (*N*-Bn), and **5h** (Reversan) were obtained by their recrystallization from methanol/ethyl acetate (1 : 3) using the slow evaporation method (Scheme 6, see ESI† for details).

Remarkable, silica gel is a heterogeneous catalyst serving challenging reactions that an acid medium could favor, such as

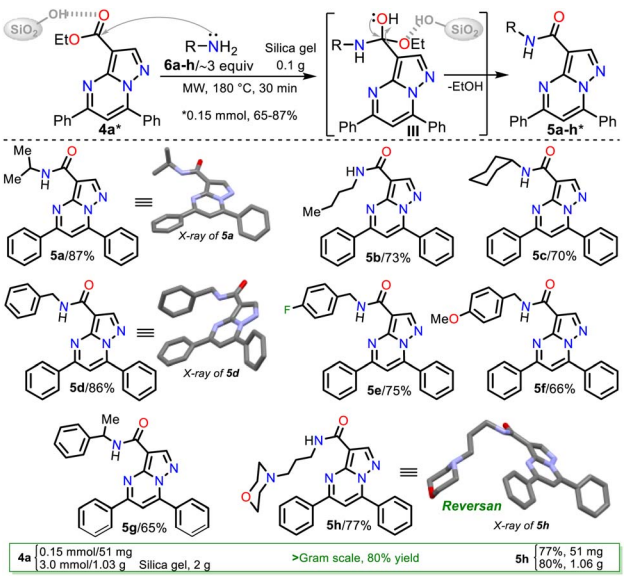
Table 2 Optimization of the synthesis of *N*-butycarboxamide **4b**[a]



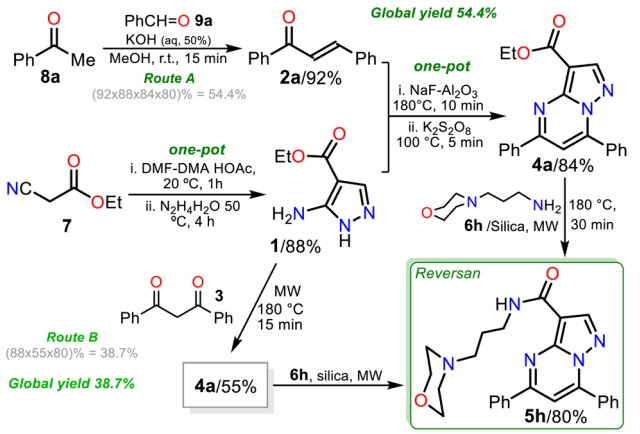
Entry	**6b** (mmol)	*T* (°C)	Time *t* (min)	Yield (%)
1	0.15	130	30	NR
2	0.15	130	60	NR
3	0.15	160	30	NR
4	0.30	130	30	NR
5	0.30	160	30	Traces
6	0.30	180	30	Traces
7	0.30	180	60	35
8	0.45	160	30	22
9	0.45	180	30	73
10	0.45	180	60	65

[a] Reactions conditions: **4a**, **6b**, and 0.1 g silica gel in a 10 mL sealed tube under MW.

the amidation reaction of esters studied in this work (see Scheme 6, at the top). In addition, due to the biological relevance and the high price of Reversan (**5h**), we obtained it on a one gram scale in high yield (80%) using 3.0 mmol ester **4a** and 9 mmol 6h (Scheme 6, data in rectangle). Thus, this synthesis is a valuable input to the scientists investigating drug discovery with biological, pharmacological, or medicinal applications because we used cheap substances (*i.e.*, 3-morpholinopropanamine (**6h**), ethyl acetoacetate (**7**), acetophenone (**8a**), benzaldehyde (**9a**), DMF-DMA, acetic acid, hydrazine, KOH, NaF, $K_2S_2O_8$, alumina, and silica gel) through simple,



Scheme 6 Synthesis of Reversan (**5h**) and its structural analogues **5a–g**.



Scheme 7 Synthesis of Reversan (**5h**) by routes A (is gram scale) and B.

highly efficient, and even scalable synthetic methodologies (Scheme 7).

Finally, pyrazolo[1,5-*a*]pyrimidine ester **4a** was also obtained by the reaction of dibenzoylmethane (**3**)[23] with pyrazole aminoester **1** in microwaves, allowing us to develop a second synthesis of Reversan (route B) to compare with the first synthesis through enone **2a** (route A). In route A, an overall yield of 54.4% was obtained in four reaction steps, while route B proceeded in three reaction steps with an overall yield of 38.7% using substrate **3**, which is relatively expensive and more difficult to prepare than **2a** (Scheme 7).[23] Consequently, route A is better than route B because the best global yield is obtained, and with compounds **4b–h**, greater structural diversity can be obtained for further studies related to Reversan and its structural analogues.

As a final comment regarding the results of this investigation, it should be noted that only one (Reversan **5h**) of the eight amides synthesized **4a–h** has been reported in the literature, and as cited in the introduction, a synthetic route for Reversan, which documents all the syntactic and characterization details, is yet to be reported.

Conclusion

In summary, Reversan (**5h**) and its structural analogues (amides **5a–g**) were synthesized by the silica-mediated direct amidation reaction between ethyl-5,7-diphenylpyrazolo[1,5-*a*]pyrimidine-3-carboxylate (**4a**) and primary amines **6a–h**. In addition, a family of ethyl-5,7-diarylpyrazolo[1,5-*a*]pyrimidine-3-carboxylates **4a–h** was obtained when aminoester 1 was cyclocondensed with chalcones **2a–h** using the NaF-alumina catalyst and as the final step, a $Na_2S_2O_8$-mediated oxidation reaction. All products were obtained in high yields *via* simple, efficient, and scalable methodologies using cheap reagents, heterogeneous catalysts such as silica gel or NaF-alumina, and solvent-free reactions in fusion or microwaves. Remarkably, the two relevant reaction types for this work (cyclocondensations of chalcones with 5-aminopyrazoles bearing an EWG and esters amidation) are protocols rarely used. In addition, the obtained compounds were characterized by spectroscopic analysis, and the structures of some intermediates and products (**4a**, **4g**, **5a**, **5d**, and **5h**) were confirmed by single-crystal X-ray diffraction analysis. Therefore, we developed synthetic methods that address some of the key points associated with green chemistry principles employing easily accessible substances.

Experimental section

Reagents and materials

The reagents and substances used in this investigation were purchased from commercial sources and used without further purification; these were weighed and handled in the air at room temperature. The reaction was monitored by thin-layer chromatography (TLC), visualized by a UV lamp (254 or 365 nm), and flash chromatography was performed on silica gel (230–400 mesh). Reactions under microwave irradiation were carried out in a sealed reaction vessel (10.0 mL, max pressure = 300 psi) containing a Teflon-coated stir bar (obtained from CEM) and were performed in a CEM Discover SP-focused MW (ν = 2.45 GHz) reactor equipped with a built-in pressure measurement sensor and a vertically-focused IR temperature sensor. Controlled temperature, power, and time settings were used. Substrates based on *NH*-5-aminopyrazoles **1** and **1′** and chalcone derivatives **2a–h** were prepared by known procedures and developed by us (see ESI† for details of the synthesis of these substrates).

The NMR spectra for this work were recorded at 400 MHz (^{1}H) and 101 MHz (^{13}C) at 298 K, and the data were recorded in $CDCl_3$ (7.26/77.05 ppm) or DMSO (2.50/39.5 ppm) using the residual nondeuterated signal for ^{1}H and the deuterated solvent signal for ^{13}C NMR as internal standards. Chemical shifts (δ) are given in parts per million (and coupling constants (J) in Hertz (Hz). The multiplicity abbreviations involve s = singlet, d = doublet, t = triplet, q = quartet, and m = multiplet (see copies of NMR spectra in Fig. S3–S31 of ESI†). Melting points were determined using a capillary melting point apparatus, and the data were uncorrected. High-resolution mass spectra (HRMS) were recorded using a Q-TOF spectrometer by electrospray ionization (ESI) (see the HRMS analysis in Fig. S32–S47 of ESI†). The X-ray intensity data were measured at 25(2) °C using CuKα radiation (λ = 1.54184 Å), by ω scans in an Agilent SuperNova, Dual, Cu at Zero, Atlas four-circle diffractometer equipped with a CCD plate detector (see ESI† for more crystallographic details).

Synthesis and characterization

Synthesis of 5,7-diarylpyrazolo[1,5-*a*]pyrimidines 4a′–c′. A mixture of 3-methyl-1*H*-pyrazol-5-amine (**1′**, 0.6 mmol, 58 mg), the respective chalcone derivative **2** (0.5 mmol), KOH (0.05 mmol 3 mg), and DMF (2.5 mL) was heated at 110 °C for 20 min under constant stirring. The mixture was then allowed to cool to room temperature, water (10 mL) was added, and the aqueous mixture was extracted with ethyl acetate (3 × 10 mL). The organic extract was dried over anhydrous Na_2SO_4, and the solvent was removed under reduced pressure. The residue was

purified by flash chromatography on silica gel (eluent: *n*-pentane/AcOEt 4 : 1 v/v) to afford products **4a′–d′** (ref. 16).

*2-Methyl-5,7-diphenylpyrazolo[1,5-a]pyrimidine (**4a′**).* By the general procedure with chalcone (**2a**, 104 mg, 0.5 mmol), **4a′** was obtained as a paled-yellow solid (50 mg, 35%, amorphous). Mp: 118–119 °C (Lit.[8] 117–118 °C). Mp 117–119 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.55 (s, 3H), 6.59 (s, 1H), 7.24 (s, 1H), 7.45–7.58 (m, 6H), 8.05–8.14 (m, 4H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.9 (CH_3), 96.4 (CH), 104.3 (CH), 127.1 (CH), 128.6 (CH), 128.8 (CH), 129.2 (CH), 130.0 (CH), 130.8 (CH), 131.6 (C), 137.7 (C), 146.1 (C), 150.6 (C), 155.4 (C), 155.7 (C) ppm. These NMR data matched previously reported data.[8]

*5,7-Bis(4-chlorophenyl)-2-methylpyrazolo[1,5-a]pyrimidine (**4b′**).* By the general procedure with the dichlorochalcone **2c** (139 mg, 0.5 mmol), **4b′** was obtained as a light greenish solid (55 mg, 31%, amorphous). Mp: 180–182 °C (Lit.[8] 179–181 °C). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.53 (s, 3H), 6.57 (s, 1H), 7.18 (s, 1H), 7.48 (d, J = 8.7 Hz, 2H), 7.55 (*d*, J = 8.7 Hz, 2H), 8.05 (*d*, J = 8.7 Hz, 4H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.9 (CH_3), 96.8 (CH), 103.8 (CH), 128.5 (CH), 129.1 (CH), 129.2 (CH), 129.9 (C), 130.7 (CH), 136.0 (C), 136.5 (C), 137.2 (C), 145.2 (C), 150.5 (C), 154.5 (C), 155.8 (C) ppm. These NMR data matched previously reported data.[8]

*2-Methyl-5,7-di-p-tolylpyrazolo[1,5-a]pyrimidine (**4c′**).* By the general procedure with dimethylchalcone **2f** (118 mg, 0.5 mmol), **4c** was obtained as a yellow solid (56 mg, 36%, amorphous). Mp: 150–151 °C (amorphous) (Lit.[16] 155–157 °C). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.43 (s, 3H), 2.46 (s, 3H), 2.52 (s, 3H), 6.54 (s, 1H), 7.21 (s, 1H), 7.31 (d, J = 8.0 Hz, 2H), 7.37 (*d*, J = 8.1 Hz, 2H), 7.98–8.01 (dd, J = 8.1 Hz, 4H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 15.0 (CH_3), 21.4 (CH_3), 21.6 (CH_3), 96.2 (CH), 104.0 (CH), 127.1 (CH), 128.9 (C), 129.2 (CH), 129.4 (CH), 139.6 (CH), 135.0 (C), 140.3 (C), 141.2 (C), 146.2 (C), 150.7 (C), 155.2 (C), 155.8 (C) ppm. These NMR data matched previously reported data.[16]

Synthesis of 3-carboethoxypyrazolo[1,5-*a*]pyrimidines 4a–h. Equimolar amounts of ethyl-5-amino-1*H*-pyrazole-4-carboxylate (**1**, 0.5 mmol, 78 mg) and the respective enone **2a–h** were thoroughly mixed at room temperature, together with 25 mg of NaF–Al_2O_3 (3 : 5, w/w), into a 10 mL sealable (Teflon screw cap) tubular reaction vessel. The mixture was heated in fusion over the solid support and catalyst at 180 °C for 10 min using a sand bath. Next, 1 equiv. $K_2S_2O_8$ (135 mg) was added, and the mixture continued heating for another 5 min at 100 °C. The resulting reaction mixture was then cooled to room temperature and extracted with ethyl acetate (3 × 10 mL). The extract was dried over anhydrous Na_2SO_4, the solvent was removed, and the crude product was purified by flash chromatography on silica gel (eluent: CH_2Cl_2) to afford the desired products **4a–h** in good yields. The recrystallization of **4a** and **4g** from methanol/AcOEt (1 : 3) afforded crystalline colorless prisms suitable for X-ray diffraction analysis.

*3-Carboethoxy-5,7-diphenylpyrazolo[1,5-a]pyrimidine (**4a**).* By the general procedure with chalcone (**2a**, 104 mg, 0.5 mmol), **4a** was obtained as a yellow solid (139 mg, 81%, amorphous). For the multigram scale, 7 mmol of reagents (*i.e.*, **1**/1.09 g, **2a**/1.46 g, NF–Al_2O_3/0.35 g, and $K_2S_2O_8$/1.89 g) and a 35 mL tubular reaction vessel were used. This compound was also obtained (95 mg, 55%) using an equimolar mixture with dibenzoylmethane (**3**, 0.5 mmol, 112 mg) as the 1,3-bis(electrophilic) substrate, which was irradiated under microwaves conditions at 180 °C for 15 min. Mp: 101–103 °C (Lit.[20] 79–81 °C). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.48 (t, J = 7.1 Hz, 3H), 4.46 (q, J = 7.1 Hz, 2H) 7.49–7.53 (m, 4H) 7.58–7.62 (m, 3H), 7.99–8.04 (m, 2H), 8.24–8.28 (m, 2H), 8.60 (s, 1H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.5 (CH_3), 60.2 (CH_2), 103.0 (C), 106.4 (CH), 127.6 (CH), 128.8 (CH), 128.9 (CH), 129.4 (CH), 130.7 (CH), 131.1 (CH), 131.4 (C), 136.5 (C), 147.7 (CH), 147.8 (C), 148.7 (C), 159.0 (C), 162.8 (C) ppm. HRMS (ESI) *m*/*z*: $[M + H]^+$ calcd for $C_{21}H_{18}N_3O_2^+$ 344.1394; found 344.1400. These data matched previously reported data using another method.[20]

*5,7-Bis(4-fluorophenyl)-3-carboethoxypyrazolo[1,5-a]pyrimidine (**4b**).* By the general procedure with difluorochalcone **2b** (122 mg, 0.5 mmol), **4b** was obtained as a yellow solid (173 mg, 91%, amorphous). Mp: 123–124 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.47 (t, J = 7.1 Hz, 3H), 4.45 (q, J = 7.1 Hz, 2H), 7.19 (t, J = 8.5 Hz, 2H), 7.29 (t, J = 8.3 Hz, 2H), 7.44 (s, 1H), 8.07 (dd, J = 8.1 Hz, 2H), 8.26 (dd, J = 8.2 Hz, 2H), 8.57 (s, 1H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): 14.5 (CH_3), 60.3 (CH_2), 103.0 (C), 105.8 (CH), 115.9/116.2 (CH, d, J = 21.7 Hz), 115.9/116.1 (CH, d, J = 21.7 Hz), 126.6 (C, d, J = 3.7 Hz), 129.8 (CH, d, J = 8.8 Hz), 131.8 (CH, d, J = 9.0 Hz), 132.6 (C, J = 3.0 Hz), 146.8 (C), 147.8 (CH), 148.8 (C), 157.8 (C), 162.7 (C), 163.2/165.7 (CF, d, J = 253.1 Hz), 163.5/166.0 (CF, d, J = 252.4 Hz) ppm. HRMS (ESI) *m*/*z*: $[M + H]^+$ calcd for $C_{21}H_{16}F_2N_3O_2^+$ 380.1205; found 380.1206.

*5,7-Bis(4-chlorophenyl)-3-carboethoxypyrazolo[1,5-a]pyrimidine (**4c**).* By the general procedure with dichlorochalcone **2c** (139 mg, 0.5 mmol), **4c** was obtained as a yellow solid (163 mg, 79%, amorphous). Mp: 175–176 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.46 (t, J = 7.1 Hz, 3H), 4.45 (q, J = 7.2 Hz, 2H), 7.45 (s, 1H), 7.48 (d, J = 8.6 Hz, 2H), 7.58 (d, J = 8.6 Hz, 2H), 8.00 (d, J = 8.6 Hz, 2H), 8.19 (d, J = 8.7 Hz, 2H), 8.57 (s, 1H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.5 (CH_3), 60.4 (CH_2), 103.3 (C), 105.8 (CH), 128.8 (C), 128.9 (CH), 129.2 (CH), 129.3 (CH), 130.8 (CH), 134.8 (C), 137.6 (C), 137.8 (C), 146.8 (C), 147.9 (CH), 148.8 (C), 157.6 (C), 162.6 (C) ppm. HRMS (ESI) *m*/*z*: $[M + H]^+$ calcd for $C_{21}H_{16}{}^{35}Cl_2N_3O_2^+$ 412.0614; found 412.0615.

*5,7-Bis(4-bromophenyl)-3-carboethoxypyrazolo[1,5-a]pyrimidine (**4d**).* By the general procedure with dibromochalcone **2d** (183 mg, 0.5 mmol), **4d** was obtained as a yellow solid (193 mg, 77%, amorphous). Mp: 123–124 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.47 (t, J = 7.1 Hz, 2H), 4.46 (q, J = 7.2 Hz, 2H), 7.47 (s, 1H), 7.67 (d, J = 8.5 Hz, 2H), 7.75 (d, J = 8.6 Hz, 2H), 7.93 (d, J = 8.5 Hz, 2H), 8.14 (d, J = 8.6 Hz, 2H), 8.59 (s, 1H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.6 (CH_3), 60.4 (CH_2), 103.4 (C), 105.8 (CH), 126.2 (C), 126.3 (C), 129.2 (CH), 129.4 (C), 131.0 (CH) 132.2 (CH), 132.3 (CH), 135.3 (C), 147.0 (C), 148.0 (CH), 148.8 (C), 157.8 (C), 162.7 (C) ppm. HRMS (ESI) *m*/*z*: $[M + H]^+$ calcd for $C_{21}H_{16}{}^{79}Br_2N_3O_2^+$ 499.9604; found 499.9606.

*5,7-Bis(4-metoxyphenyl)-3-carboethoxypyrazolo[1,5-a]pyrimidine (**4e**).* By the general procedure with dimethoxychalcone **2e** (134 mg, 0.5 mmol), **4e** was obtained as a yellow solid (161 mg, 80%, amorphous). Mp: 175–176 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.47 (t, J = 7.2 Hz, 3H), 3.88 (s, 3H), 3.90 (s, 3H), 4.45 (q, J =

7.2 Hz, 2H), 7.01 (d, J = 8.7 Hz, 2H), 7.09 (d, J = 8.8 Hz, 2H), 7.42 (s, 1H), 8.03 (d, J = 8.7 Hz, 2H), 8.23 (d, J = 8.7 Hz, 2H), 8.55 (s, 1H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.6 (CH_3), 55.4 (CH_3), 55.5 (CH_3), 60.1 (CH_2), 102.3 (C), 105.1 (CH), 114.2 (CH), 114.3 (CH), 122.9 (C), 129.1 (C), 129.3 (CH), 131.2 (CH), 147.4 (C), 147.5 (CH), 149.1 (C), 158.5 (C), 161.9 (C), 162.1 (C), 163.0 (C) ppm. HRMS (ESI): $[M + H]^+$ calcd for $C_{23}H_{22}N_3O_4^+$ 404.1605; found 404.1611.

*3-Carboethoxy-5,7-di-p-tolylpyrazolo[1,5-a]pyrimidine (**4f**).* By the general procedure with dimethyl-chalcone **2f** (118 mg, 0.5 mmol), **4f** was obtained as a yellow solid (139 mg, 75%, amorphous). Mp: 130–132 °C (Lit.[20] 129–131 °C). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.48 (t, J = 7.2 Hz, 3H), 2.45 (s, 3H), 2.48 (s, 3H), 4.46 (q, J = 7.2 Hz, 2H), 7.34 (d, J = 8.2 Hz, 2H), 7.41 (d, J = 8.2 Hz, 2H), 7.49 (s, 1H), 7.93 (d, J = 8.1 Hz, 2H), 8.18 (d, J = 8.2 Hz, 2H), 8.57 (s, 1H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.6 (CH_3), 21.5 (CH_3), 21.6 (CH_3), 60.2 (CH_2), 102.7 (C), 105.9 (CH), 127.6 (CH), 127.9 (C), 129.4 (CH), 129.5 (CH), 129.8 (CH), 133.9 (C), 141.7 (C), 142.0 (C), 147.7 (CH), 147.9 (C), 149.0 (C), 159.0 (C), 163.0 (C) ppm. HRMS (ESI): $[M + H]^+$ calcd for $C_{23}H_{22}N_3O_2^+$ 372.1707; found 372.1708. These data matched previously reported data.[20]

*3-Carboethoxy-5-(4-chlorophenyl)-7-(p-tolyl)pyrazolo[1,5-a] pyrimidine (**4g**).* This ester was obtained, following the general procedure with (*E*)-1-(4-chlorophenyl)-3-(*p*-tolyl)propen-1-one (**2g**, 128 mg, 0.5 mmol), as a yellow solid (116 mg, 59%, amorphous). Mp: 163–164 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.47 (t, J = 7.2 Hz, 3H), 2.48 (s, 3H), 4.46 (q, J = 7.0 Hz, 2H), 7.42 (d, J = 8.3 Hz, 2H), 7.47 (s, 1H), 7.51 (d, J = 8.7 Hz, 2H), 7.94 (d, J = 8.2 Hz, 2H), 8.23 (d, J = 8.7 Hz, 2H), 8.59 (s, 1H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.5 (CH_3), 21.6 (CH_3), 60.3 (CH_2), 103.0 (C), 105.7 (CH), 127.6 (C), 128.9 (CH), 129.2 (CH), 129.4 (CH), 129.5 (CH), 135.1 (C), 137.4 (C), 142.2 (C), 147.8 (CH), 148.2 (C), 148.9 (C), 157.6 (C), 162.8 (C) ppm. HRMS (ESI): $[M + H]^+$ calcd for $C_{22}H_{18}ClN_3O^+$ 392.1160; found 371. 392.1179.

*3-Carboethoxy-7-(4-chlorophenyl)-5-(p-tolyl)pyrazolo[1,5-a] pyrimidine (**4h**).* This ester was obtained, following the general process with (*E*)-3-(4-chlorophenyl)-1-(*p*-tolyl)propen-1-one (**2h**, 128 mg, 0.5 mmol), as a yellow solid (106 mg, 54%, amorphous). Mp: 150–151 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.48 (t, J = 7.1 Hz, 3H), 2.45 (s, 3H), 4.46 (q, J = 7.1 Hz, 2H), 7.35 (d, J = 8.3 Hz, 2H), 7.49 (s, 1H), 7.59 (d, J = 7.0 Hz, 2H), 8.00 (d, J = 8.6 Hz, 2H), 8.18 (d, J = 7.0 Hz, 2H), 8.57 (s, 1H) ppm.^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.6 (CH_3), 21.6 (CH_3), 60.3 (CH_2), 103.0 (C), 106.0 (CH), 127.6 (CH), 129.2 (CH), 129.8 (CH), 130.9 (CH), 133.7 (C), 137.7 (C), 141.9 (C), 146.6 (C), 147.8 (CH), 149.0 (C), 159.1 (C), 162.9 (C) ppm. HRMS (ESI^+): $[M + H]^+$ calcd for $C_{22}H_{18}ClN_3O^+$ 392.1160; found 371. 392.1163.

Synthesis of *N*-alkyl-3-carbamoylpyrazolo[1,5-*a*]pyrimidines 5a–h. A mixture of 3-carboethoxy-5,7-diphenylpyrazolo[1,5-*a*] pyrimidine (**4a**, 51 mg, 0.15 mmol) and an excess of primary alkylamine **6a–h** (~3 equiv.) was dissolved in ethyl ether (1 mL); then, silica gel (230–400 mesh, 100 mg) was added, thoroughly mixing all components at room temperature. After removing the ether, the solid residue was subjected to microwave irradiation at 180 °C (200 W, monitored by an IR temperature sensor) and maintained at this temperature for 30 min in a sealed MW tube of 10 mL. The resulting mixture was cooled to room temperature by airflow, ethyl acetate was added (3.0 mL), and sonicated for 20 min; this mixture was filtered, the solid residue was washed with ethyl acetate (3.0 mL), and the organic phase was washed with a saturated solution of $NaHCO_3$ and HCl 10%. The organic extract was dried over anhydrous Na_2SO_4, filtered, and the solvent was removed under reduced pressure. The residue was purified by flash chromatography on silica gel (eluent: CH_2Cl_2/MeOH 30 : 1 v/v) to afford products **5a–h** in good yields. The recrystallization of amides **5a**, **5d**, and **5h** from methanol/ethyl acetate (1 : 3) afforded crystalline colorless prisms suitable for X-ray diffraction analysis.

*N-Isopropyl-5,7-diphenylpyrazolo[1,5-a]pyrimidine-3-carboxamide (**5a**).* By the general procedure with isopropylamine (**6a**, 30 mg, 0.50 mmol), **5a** was obtained as a pale greenish solid (46.5 mg, 87%, amorphous). Mp: 203–204 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.38 (d, J = 6.5 Hz, 6H), 4.38 (m, 1H), 7.48 (s, 1H), 7.56–7.64 (m, 6H), 8.04–8.17 (m, 4H), 8.25 (d, J = 7.5 Hz, NH), 8.71 (s, 1H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 23.2 (CH_3), 40.9 (CH), 105.7 (CH), 106.1 (C), 127.2 (CH), 128.8 (CH), 129.2 (CH), 129.4 (CH), 130.5 (C), 131.2 (CH), 131.6 (CH), 136.4 (C), 146.8 (C), 146.9 (CH), 148.2 (C), 157.6 (C), 161.6 (C) ppm. HRMS (ESI^+): $[M + H]^+$ calcd for $C_{23}H_{21}N_4O^+$ 357.1710; found 357.1709.

*N-Butyl-5,7-diphenylpyrazolo[1,5-a]pyrimidine-3-carboxamide (**5b**).* By the general procedure with *n*-butylamine (**6b**, 33 mg, 0.45 mmol), **5b** was obtained as a brown solid (41 mg, 73%, amorphous). Mp: 97–99 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.03 (t, J = 7.3 Hz, 3H), 1.56 (m, 2H), 1.72 (m, 2H), 3.59 (q, J = 6.8 Hz, 2H), 7.49 (s, 1H), 7.56–7.67 (m, 6H), 8.03–8.17 (m, 4H), 8.31 (t, J = 5.4 Hz, NH), 8.72 (s, 1H, H2) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.9 (CH_3), 20.3 (CH), 31.8 (CH_2), 38.7 (CH_2), 105.9 (C), 106.1 (CH), 127.4 (CH), 128.9 (CH), 129.2 (CH), 129.4 (CH), 130.5 (C), 131.2 (CH), 131.6 (CH), 136.5 (C), 146.8 (C), 147.0 (CH), 148.2 (C), 157.8 (C), 162.4 (C) ppm. HRMS (ESI^+): $[M + H]^+$ calcd for $C_{23}H_{23}N_4O^+$ 371.1866; found 371.1896.

*N-Cyclohexyl-5,7-diphenylpyrazolo[1,5-a]pyrimidine-3-carboxamide (**5c**).* By the general procedure (200 °C, 30 min × 4) with cyclohexylamine (**6c**, 50 mg, 0.50 mmol), **5c** was obtained as a yellow solid (42 mg, 70%, amorphous). Mp: 188–190 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.26–1.57 (m, 5H), 1.67 (m, 1H), 1.80 (m, 2H), 2.10 (m, 2H), 4.15 (m, 1H), 7.48 (s, 1H), 7.56–7.63 (m, 6H), 8.04–8.16 (m, 4H), 8.35 (d, J = 8.1 Hz, NH), 8.71 (s, 1H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 24.5 (CH_2), 25.8 (CH_2), 33.2 (CH_2), 47.3 (CH), 105.9 (CH), 106.3 (C), 127.4 (CH), 128.9 (CH), 129.3 (CH), 129.5 (CH), 130.6 (C), 131.2 (CH), 131.6 (CH), 136.6 (C), 146.9 (C), 147.1 (CH), 148.3 (C), 157.7 (C), 161.5 (C). HRMS (ESI^+): $[M + H]^+$ calcd for $C_{25}H_{25}N_4O^+$ 397.2023; found 397.2031.

*N-Benzyl-5,7-diphenylpyrazolo[1,5-a]pyrimidine-3-carboxamide (**5d**).* By the general procedure with benzylamine (**6d**, 50 mg, 0.47 mmol), **5d** was obtained as a pale greenish solid (52.2 mg, 86%, amorphous). Mp: 208–209 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.77 (d, J = 5.4 Hz, 2H), 7.32–7.56 (m, 9H), 7.63 (m, 3H), 7.95 (d, J = 8.0 Hz, 2H), 8.07 (m, 2H), 8.66 (t, J = 5.4 Hz, 1H), 8.75 (s, 1H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 43.6 (CH_2), 105.7 (C), 105.8 (CH), 127.3 (CH), 127.4 (CH), 127.9 (CH), 128.8 (CH), 128.9

(CH), 129.1 (CH), 129.4 (CH), 130.5 (C), 131.2 (CH), 131.6 (CH), 136.1 (C), 138.7 (C), 146.9 (CH), 147.1 (C), 148.3 (C), 157.7 (C), 162.3 (C) ppm. HRMS (ESI^+): $[M + H]^+$ calcd for $C_{26}H_{21}N_4O^+$ 405.1710; found 405.1710.

*N-(4-Fluorobenzyl)-5,7-diphenylpyrazolo[1,5-a]pyrimidine-3-carboxamide (**5e**).* By the general procedure (30 min × 3) with 4-flurorobenzylamine (**6e**, 60 mg, 0.48 mmol), **5e** was obtained as a yellow solid (47.5 mg, 75%, amorphous). Mp: 77–78 °C. ^1H NMR (400 MHz, $CDCl_3$): $\delta = 4.72$ (d, $J = 5.3$ Hz, 2H), 7.09 (t, $J =$ 8.7 Hz, 2H), 7.43–7.50 (m, 5H), 7.55 (t, $J = 7.2$ Hz, 1H), 7.62 (m, 3H), 7.94 (d, $J = 8.0$ Hz, 2H), 8.06 (m, 2H), 8.64 (t, $J = 5.4$ Hz, NH), 8.73 (s, 1H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 42.9$ (CH_3), 105.6 (C), 105.9 (CH), 115.5/115.7 (CH, d, $J = 21.6$ Hz), 127.3 (CH), 128.9 (CH), 129.2 (CH), 129.5 (CH), 129.6/129.7 (CH, $J = 8.1$ Hz), 130.4 (C), 131.4 (CH), 131.7 (CH), 134.6 (C, d, $J = 3.3$ Hz), 136.1 (C), 146.9 (CH), 147.1 (C), 148.4 (C), 157.8 (C), 163.4/161.0 (CF, d, $J = 245.4$ Hz), 162.3 (C) ppm. HRMS (ESI^+): $[M + H]^+$ calcd for $C_{26}H_{20}N_4O^+$ 423.1616; found 419.1615.

*N-(4-Methoxybenzyl)-5,7-diphenylpyrazolo[1,5-a]pyrimidine-3-carboxamide (**5f**).* By the general procedure (30 min × 2) with 4-methoxybenzylamine (**6f**, 65 mg, 0.47 mmol), **5f** was obtained as an orange solid (43 mg, 66%, amorphous). Mp: 171–172 °C. ^1H NMR (400 MHz, $CDCl_3$): $\delta = 3.84$ (s, 3H), 4.68 (d, $J = 5.1$ Hz, 2H), 6.94 (d, $J = 8.8$ Hz, 2H), 7.38–7.48 (m, 4H), 7.52 (t, $J = 7.2$ Hz, 1H), 7.59–7.65 (m, 3H), 7.92 (d, $J = 8.3$ Hz, 2H), 8.03–8.07 (m, 2H), 8.60 (t, $J = 5.0$ Hz, 1H), 8.73 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 43.1$ (CH_3), 55.3 (CH_2), 105.7 (CH), 105.8 (C), 114.1 (CH), 127.3 (CH), 128.9 (CH), 129.1 (CH), 129.3 (CH), 129.4 (CH), 130.4 (C), 130.8 (C), 131.3 (CH), 131.6 (CH), 136.0 (C), 146.9 (CH), 147.0 (C), 148.3 (C), 157.6 (C), 159.0 (C), 162.2 (C). HRMS (ESI^+): $[M + H]^+$ calcd for $C_{27}H_{23}N_4O^+$ 435.1816; found 435.1831.

*5,7-Diphenyl-N-(1-phenylethyl)pyrazolo[1,5-a]pyrimidine-3-carboxamide (**5g**).* By the general procedure with 1-phenyl-ethanamine (**6g**, 60 mg, 0.49 mmol), **5g** was obtained as a yellow solid (40.8 mg, 65%, amorphous). Mp: 75–76 °C. ^1H NMR (400 MHz, $CDCl_3$): $\delta = 1.71$ (d, $J = 6.8$ Hz, 3H), 5.40 (m, 1H), 7.33 (t, $J = 7.2$ Hz, 1H), 7.41 (t, $J = 7.6$ Hz, 2H) 7.48 (s, 1H), 7.50–763 (m, 8H), 7.99–8.08 (m, 4H), 8.71 (s, 1H), 8.75 (d, $J =$ 7.5 Hz, NH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 22.7$ (CH_3), 49.0 (CH), 105.8 (CH), 105.9 (C), 126.45 (CH), 127.3 (CH), 127.4 (CH), 128.8 (CH), 128.9 (CH), 129.2 (CH), 129.4 (CH), 130.5 (C), 131.3 (CH), 131.7 (CH), 136.2 (C), 143.9 (C), 146.9 (C), 147.0 (C), 148.3 (C), 157.7 (C), 161.6 (C) ppm. HRMS (ESI^+): $[M + H]^+$ calcd for $C_{27}H_{23}N_4O^+$ 419.1866; found 419.1864.

*N-(3-morpholinopropyl)-5,7-diphenylpyrazolo[1,5-a]pyrimidine-3-carboxamide (**5h**).* By the general procedure with 3-morpholino-propanamine (**6h**, 70 mg, 0.48 mmol), Reversan (**5h**) was obtained as a yellow solid (51 mg, 77%, amorphous). For the one gram scale, 3 mmol of **1a** (1.03 g), 9 mmol of **2h** (1.3 g), and a 35 mL tubular reaction vessel were used (1.06 g, 80%). Mp: 94–95 °C. ^1H NMR (400 MHz, $CDCl_3$): $\delta = 1.92$ (m, $J =$ 6.9 Hz, 2H), 2.46 (m, 4H), 2.53 (t, $J = 7.3$ Hz, 2H), 3.61–3.70 (m, 6H), 7.49 (s, 1H), 7.54–7.64 (m, 6H), 8.04–8.16 (m, 4H), 8.34 (t, J = 6.2 Hz, NH), 8.72 (s, 1H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): $\delta =$ 27.0 (CH_2), 37.3 (CH_2), 53.8 (CH_2), 56.6 (CH_2), 67.0 (CH_2), 106.0 (C), 106.1 (CH), 127.5 (CH), 129.0 (CH), 129.3 (CH), 129.5 (CH), 130.5 (C), 131.4 (CH), 131.8 (CH), 136.6 (C), 147.0 (C), 147.1 (C2), 148.4 (C), 158.0 (C), 162.5 (C) ppm. HRMS (ESI^+): $[M + H]^+$ calcd for $C_{26}H_{27}N_5O_2^+$ 442.2238; found 442.2253.

Conflicts of interest

The authors declare no competing financial interest.

Author contributions

Individuals listed as authors have contributed to developing this manuscript, and no other person was involved with its progress. The authors' contributions included: A. A.-G. carried out all the experiments and literature review, M.-A. M the X-ray diffraction studies and their respective analysis, and J. P. the composition of original draft, supervision, and sources. All authors have read and agreed to the published version of this paper.

Acknowledgements

We thank the Department of Chemistry, Science Faculty, and Vicerrectoría de Investigaciones at the Universidad de Los Andes for financial support. We also acknowledge Sandra Ortiz of Universidad de Los Andes for acquiring the mass spectra.

Notes and references

1 Z.-X. He, T.-Q. Zhao, Y.-P. Gong, X. Zhang, L.-Y. Ma and H.-M. Liu, *Eur. J. Med. Chem.*, 2020, **200**, 112458.
2 M. S. Pote and R. N. Gacche, *Drug Discovery*, 2023, 103537.
3 A. H. Schinkel and J. W. Jonker, *Adv. Drug Delivery Rev.*, 2012, **64**, 138–153.
4 C. C. Gana, K. M. Hanssen, D. M. T. Yu, C. L. Flemming, M. S. Wheatley, G. Conseil, S. P. C. Cole, M. D. Norris, M. Haber and J. I. Fletcher, *Biochem. Pharmacol.*, 2019, **168**, 237–248.
5 K. M. Hanssen, M. Haber and J. I. Fletcher, *Drug Resistance Updates*, 2021, **59**, 100795.
6 C. A. Burkhart, F. Watt, J. Murray, M. Pajic, A. Prokvolit, C. Xue, C. Flemming, J. Smith, A. Purmal, N. Isachenko, P. G. Komarov, K. V. Gurova, A. C. Sartorelli, G. M. Marshall, M. D. Norris, A. V. Gudkov and M. Haber, *Cancer Res.*, 2009, **69**, 6573–6580.
7 J.-C. Castillo, H.-A. Rosero and J. Portilla, *RSC Adv.*, 2017, **7**, 28483–28488.
8 S.-L. Aranzazu, A. Tigreros, A. Arias-Gómez, J. Zapata-Rivera and J. Portilla, *J. Org. Chem.*, 2022, **87**, 9839–9850.
9 A. Tigreros, M. Macías and J. Portilla, *ChemPhotoChem*, 2022, **6**, e202200133.
10 A. Tigreros and J. Portilla, *Eur. J. Org. Chem.*, 2022, **2022**, e202200249.
11 A. Arias-Gómez, A. Godoy and J. Portilla, *Molecules*, 2021, **26**, 2708.
12 A. Al-Azmi, *Curr. Org. Chem.*, 2019, **23**, 721–743.
13 S. Cherukupalli, R. Karpoormath, B. Chandrasekaran, G. A. Hampannavar, N. Thapliyal and V. N. Palakollu, *Eur. J. Med. Chem.*, 2017, **126**, 298–352.

14 T. S. Saleh and A. S. Al-Bogami, *Heterocycles*, 2016, **92**, 2066–2077.
15 V. D. Orlov, J. Quiroga, N. N. Kolos and S. M. Desenko, *Chem. Heterocycl. Compd.*, 1988, 962–965.
16 P. Kaswan, K. Pericherla, D. Purohit and A. Kumar, *Tetrahedron Lett.*, 2015, **56**, 549–553.
17 A. Tigreros, J. C. Castillo and J. Portilla, *Talanta*, 2020, **215**, 120905.
18 L. Yin and J. Liebscher, *Synthesis (Stuttg)*, 2004, **2004**, 2329–2334.
19 M.-C. Ríos and J. Portilla, *Chemistry (Easton)*, 2022, **4**, 940–968.
20 P. M. Kumar, K. S. Kumar, P. K. Mohakhud, K. Mukkanti, R. Kapavarapu, K. V. L. Parsa and M. Pal, *Chem. Commun.*, 2012, **48**, 431–433.
21 N. Suresh, B. V. Durgarao, A. Ratnakar, S. K. Kolli, M. A. Ashfaq, M. V. Basaveswara Rao and M. Pal, *Lett. Drug Des. Discovery.*, 2017, **14**, 1176–1183.
22 V. V. Lipson, S. M. Desenko, V. V. Borodina and M. G. Shirobokova, *Chem. Heterocycl. Compd.*, 2007, **43**, 1544–1550.
23 M. Yoshida, A. Mori, A. Inaba, M. Oka, H. Makino, M. Yamaguchi, H. Fujita, T. Kawamoto, M. Goto, H. Kimura, A. Baba and T. Yasuma, *Bioorg. Med. Chem.*, 2010, **18**, 8501–8511.
24 C. A. Faler and M. M. Joullié, *Tetrahedron Lett.*, 2006, **47**, 7229–7231.
25 T. Yamada, Y. Watanabe and S. Okamoto, *RSC Adv.*, 2021, **11**, 24588–24593.
26 X. Wu, L. Zhou, F. Li and J. Xiao, *J. Chem. Res.*, 2021, **45**, 491–497.
27 S. Zeng, J. Liu, S. Anankanbil, M. Chen, Z. Guo, J. P. Adams, R. Snajdrova and Z. Li, *ACS Catal.*, 2018, **8**, 8856–8865.
28 C. Duangkamol, S. Jaita, S. Wangngae, W. Phakhodee and M. Pattarawarapan, *RSC Adv.*, 2015, **5**, 52624–52628.
29 N. Martín and F. G. Cirujano, *Catal. Commun.*, 2022, **164**, 106420.
30 J. I. Levin, E. Turos and S. M. Weinreb, *Synth. Commun.*, 1982, **12**, 989–993.
31 S. Ghosh, A. Bhaumik, J. Mondal, A. Mallik, S. Sengupta (Bandyopadhyay) and C. Mukhopadhyay, *Green Chem.*, 2012, **14**, 3220–3229.
32 B. Nammalwar, N. P. Muddala, F. M. Watts and R. A. Bunce, *Tetrahedron*, 2015, **71**, 9101–9111.
33 A. Ojeda-Porras, A. Hernández-Santana and D. Gamba-Sánchez, *Green Chem.*, 2015, **17**, 3157–3163.
34 M. C. Witschel, H. W. Höffken, M. Seet, L. Parra, T. Mietzner, F. Thater, R. Niggeweg, F. Röhl, B. Illarionov, F. Rohdich, J. Kaiser, M. Fischer, A. Bacher and F. Diederich, *Angew. Chem., Int. Ed.*, 2011, **50**, 7931–7935.
35 S. Patnaik, W. Zheng, J. H. Choi, O. Motabar, N. Southall, W. Westbroek, W. A. Lea, A. Velayati, E. Goldin, E. Sidransky, W. Leister and J. J. Marugan, *J. Med. Chem.*, 2012, **55**, 5734–5748.
36 S. M. Bronner, J. Murray, F. A. Romero, K. W. Lai, V. Tsui, P. Cyr, M. H. Beresini, G. de leon Boenig, Z. Chen, E. F. Choo, K. R. Clark, T. D. Crawford, H. Jayaram, S. Kaufman, R. Li, Y. Li, J. Liao, X. Liang, W. Liu, J. Ly, J. Maher, J. Wai, F. Wang, A. Zheng, X. Zhu and S. Magnuson, *J. Med. Chem.*, 2017, **60**, 10151–10171.
37 A. K. Ajeesh Kumar, K. B. Nair, Y. D. Bodke, G. Sambasivam and K. G. Bhat, *Monatsh. Chem.*, 2016, **147**, 2221–2234.
38 G. D. Yadav and D. P. Wagh, *ChemistrySelect*, 2020, **5**, 9059–9085.
39 N. L. Nam, I. I. Grandberg and V. I. Sorokin, *Chem. Heterocycl. Compd.*, 2002, **38**, 1371–1374.
40 M.-C. Ortiz and J. Portilla, *Targets Heterocycl. Syst.*, 2021, **25**, 436–462.
41 K. Tanabe, in *Solid Acids and Bases: Their Catalytic Properties*, Academic Press Inc., Elsevier, London, 1970, ch. 4, pp. 45–101.
42 K. Tanabe, in *Solid Acids and Bases*, Academic Press Inc., Elsevier, London, 1970, ch. 5, pp. 103–158.
43 J. T. Sarmiento and J. Portilla, *Curr. Org. Synth.*, 2023, **20**, 77–95.
44 P. J. Chupas and C. P. Grey, *J. Catal.*, 2004, **224**, 69–79.
45 F. Kenari, S. Molnár, I. D. Borges, H. B. Napolitano and P. Perjési, *Int. J. Mol. Sci.*, 2023, **24**, 8557.
46 N. R. Candeias, L. C. Branco, P. M. P. Gois, C. A. M. Afonso and A. F. Trindade, *Chem. Rev.*, 2009, **109**, 2703–2802.