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Lewis Acid-Catalyzed Generation of C–C and C–N Bonds on π-Deficient Heterocyclic Substrates

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Abstract: Focused microwave irradiation of a series of halogenated nitrogen heterocycles and different kinds of nucleophiles in the presence of a catalytic amount of indium trichloride leads to the efficient and completely regioselective generation of aromatic C–C and C–N bonds. The method is simple, rapid, general and inexpensive, and can be performed without the use of dried solvents. Most of the synthetized compounds are new and in many cases the work-up required only filtration. Furthermore, this is the first example of the use of a Lewis acid as a catalyst for heteroarylation, vinylation and amination reactions on π-deficient heterocyclic substrates.

Keywords: C–C bond formation; C–N bond formation; cross-coupling; heteroarylation; Lewis acids; microwave-assisted synthesis

Introduction

Nitrogen heterocycles are crucial for the pharmaceutical and agrochemical industries.[1,2] Cross-coupling reactions able to generate carbon-carbon (C–C) and carbon-nitrogen (C–N) bonds on nitrogen heterocyclic substrates are of great importance in the synthesis of a large variety of bioactive compounds. Some examples include indolylquinolines, which play an important structural role in several biological processes and have been shown to possess antileishmanial and antibacterial activities,[3] derivatives of the quinazoline and acridine nuclei with anticancer,[4,5] antimalarial[6] and a variety of other pharmacological activities,[7] and derivatives of quinoxaline,[8] purine,[9] pyridine[10] and benzimidazole,[11] also with a considerable biomedical interest. Some representative examples are shown in Figure 1.

To date, transition metal-catalyzed cross-coupling has been the most employed method for the generation of both C–N and C–C bonds on heterocyclic substrates. However, Buchwald–Hartwig, Suzuki–Miyaura and related reactions require the use of expensive and cumbersome catalysts and phosphine ligands, which becomes an important issue in industrial settings.[12] In the particular case of C–C bond formation, substantial efforts have been made to achieve the coupling between heteroarenes and aza-aromatic compounds, and several methods have been described that include: (i) the use of organolithium or organomagnesium reagents, which are problematic owing to their pyrophoric nature and the need for low temperatures in many cases;[13] (ii) the multistep construction of the chemical moiety to be attached to the heterocycle;[14] (iii) the use of more contrived methods requiring specialized equipment such as photochemical[15] and electrochemical[16] reactions; (iv) 2-(3-indolyl-) and 2-(2-pyrrolyl)quinolines can be prepared by carrying out the reaction in the presence of Brønsted acids. This method requires high temperatures and long reaction times and gives only moderate yields,[17] although it has the advantage of not needing Cl-activation of the substrate. One example of a 4-(3-indolylquinoline) was prepared, albeit under quite harsh conditions, by melting together at 140 °C the starting indole and 4-chloroquinoline derivatives in the presence of *N*-methyl-2-pyrrolidinone.[18] Unfortunately, these methods are far from being general and are only appropriate for the preparation of specific compounds.

Another approach involves addition–elimination reactions between a halogenated nitrogen heterocycle and heteroarenes in the presence at least of one equivalent of the corrosive and irritating $AlCl_3$ in di-

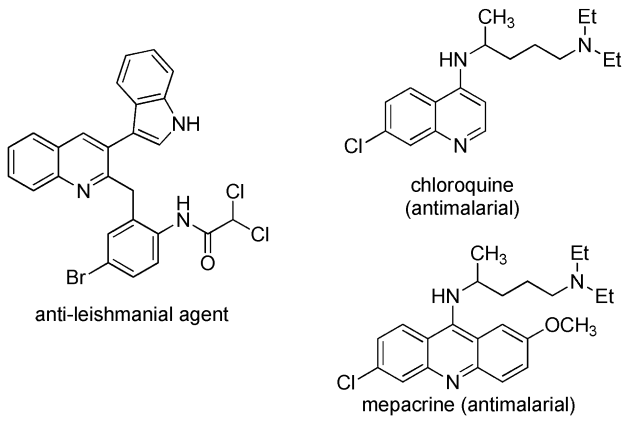


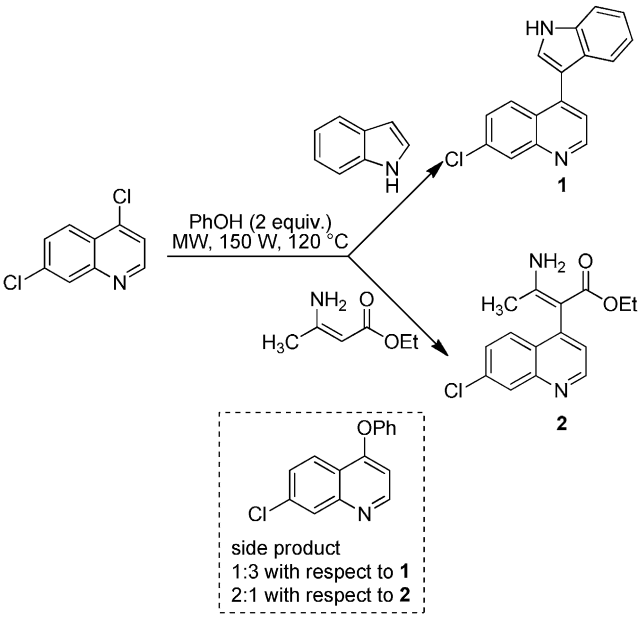
Figure 1. Examples of pharmacologically relevant compounds arising from the generation of C–C or C–N bonds on a π-deficient heterocyclic substrate

chloroethane. Such a protocol works only if the carbon bearing the halogen is strongly activated by electron-withdrawing substituents as in the case of 1,4-dichlorophthalazine, 2,4-dichloroquinazoline and 3-nitro(cyano)-2-chloropyridine.[19] Indeed, the coupling failed for 4-chloroquinoline, the presence of two trifluoromethyl groups in the quinoline core being necessary for it to take place.[19c] Therefore, these conditions are not a general arylation reaction. In fact, the development of a method useful for both the amination and (hetero)arylation of nitrogen heterocycles still represents an interesting challenge, with a great practical relevance.

In the work presented here, we show that the use of a catalytic amount of $InCl_3$ promotes cross-coupling processes between carbon nucleophiles and halides derived from π-deficient nitrogen heterocycles, allowing the efficient generation of aromatic C–C bonds in a simple and economical way. We have also found that this protocol can be extended to the amination of nitrogen heterocycles *via* C–N bond formation.

Results and Discussion

Our study started with the preparation of the indolylquinoline framework by treating 4,7-dichloroquinoline with indole under conditions previously developed for amination reactions (see below) that involve the use of phenol as a promoter, acting by protonating the quinoline nitrogen and thus increasing the electrophilicity of the halogenated C-4 position. We obtained the desired compound **1**, together with a side product derived from 4-phenoxyquinoline in a 3:1 ratio. Unfortunately, in the case of a less reactive nucleophile such as ethyl 3-aminocrotonate, the phenoxy derivative was the main reaction product (Scheme 1).



Scheme 1. Coupling reaction in the presence of phenol between 4,7-dichloroquinoline and indole or ethyl 3-aminocrotonate.

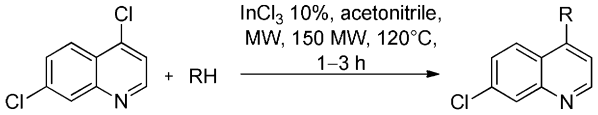
In an effort to avoid the formation of this undesired side product, we planned to replace phenol by a non-nucleophilic catalyst. Because of the near absence of precedent for the use of Lewis acids for this purpose, we were attracted to the study of this type of catalysts. We focused again on 4,7-dichloroquinoline, which constitutes the core of many pharmacological active compounds and is commercially available. In our first experiments, several Lewis acids, including CAN (cerium ammonium nitrate) and ytterbium(III) triflate, were assayed unsuccessfully. Subsequent work gave positive results with indium triflate, gallium trichloride, boron trifluoride etherate and indium trichloride. After discarding the highly hygroscopic $In(OTf)_3$ and $GaCl_3$, we chose $InCl_3$ for subsequent work because this catalyst is inexpensive, relatively stable and gave a slightly higher yield than $BF_3{\cdot}Et_2O$. The best conditions were found to involve the reaction between equimolecular amounts of 4,7-dichloroquinoline and indole and 10 mol% of $InCl_3$ in acetonitrile under focused microwave irradiation at 150 W and 120 °C for 2 h to furnish **1** as the only product in 89% yield. Since we did not employ rigorously dried solvents, it is likely that the catalyst experiences some hydrolysis under the reaction conditions. We therefore examined the catalytic effect of $In(OH)_3$ and In_2O_3, the likely hydrolysis products, but found them to be inactive (Table 1).

This protocol worked equally well for other nucleophilic heterocycles such as 4-hydroxycoumarin (**3**), for which only one hour was needed after increasing the temperature to 140 °C, and pyrrole (**5**). In the case of

Table 1. Catalyst optimization.[a]

Catalyst (10 mol%)	Yield [%]
CAN	0
$Yb(OTf)_3$	0
$In(OTf)_3$	83
$GaCl_3$	84
$BF_3{\cdot}Et_2O$	82
$InCl_3$	89
In_2O	0
$In(OH)_3$	0

[a] *Reaction conditions:* acetonitrile, MW, 150 W, 120 °C, 180 psi, 2 h.



Scheme 2. C–C coupling reactions of 4,7-dichloroquinoline.

2-methylfuran (**4**), the reaction was carried during 3 h in dichloromethane. Furthermore, a series of β-enamino esters, prepared according to literature reports,[20] reacted with quinoline to give the novel vinylation products **2** and **6–10**, which are of interest in view of the important role of β-enaminones as starting materials for synthesis.[21,22] The isolated yields were in the 71–96% range, and the method was more efficient than the previously mentioned one based on the use of $AlCl_3$ in that only catalytic amounts of $InCl_3$ were required and, furthermore, the activation of the quinoline ring by the introduction of strong electron-withdrawing groups[19c] was not necessary (Scheme 2 and Figure 2).

For comparison purposes, we carried out a few of our reactions under reflux conditions and also by heating in a sealed tube at 120 °C, which mimicked more closely the temperature conditions existing in the microwave experiments. We found dramatic differences in favour of the microwave-assisted protocol in terms of both yields and decreased reaction times (Table 2).

These encouraging results prompted us to extend the $InCl_3$-catalyzed method to other heterocyclic substrates, starting with 6,9-dichloro-2-methoxyacridine, whose choice was prompted by the pharmacological importance of acridine derivatives.[2] These new reactions showed a similar scope to the ones starting from 4,7-dichloroquinoline, and afforded the target acridine derivatives **11–15** in excellent 84–93% isolated yields (Figure 3). Finally, we also investigated the formation of C–C bonds at two other pharmaceutically relevant heterocyclic substrates, such as quinazoline and quinoxaline.[8] As shown in Figure 4, the results obtained were again satisfactory, and these reactions allowed

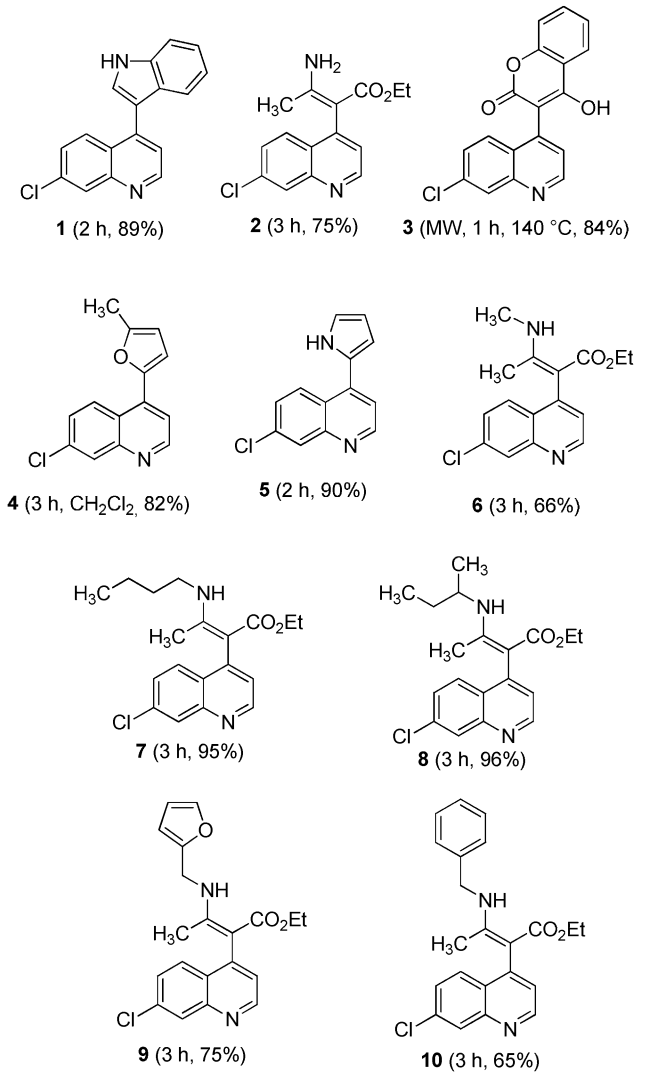


Figure 2. C–C bond forming reactions at the quinoline C-4 position.

Table 2. Comparison of heating methods.

Compound	Reflux	Sealed tube heating (120 °C)	MW
1	–	15 h, 69%	2 h, 89%
2	3 d, 45%	24 h, 25%	3 h, 82%
3	1 d, 62%	–	1 h, 84%[a]
5	1 d, 50%	15 h, 72%	2 h, 90%
9	1 d, 27%	15 h, 45%	3 h, 87%

[a] This experiment was performed at 140 °C

the preparation of compounds **16–22**. 2-(3-Indolyl)-quinoxaline **21** had been previously prepared in 47% overall yield *via* a multistep sequence based on the construction of the quinoxaline ring from an indole ketoaldehyde precursor,[14d] or in two steps and 58% overall yield from 3-acetylindole.[14c] Rather surpris-

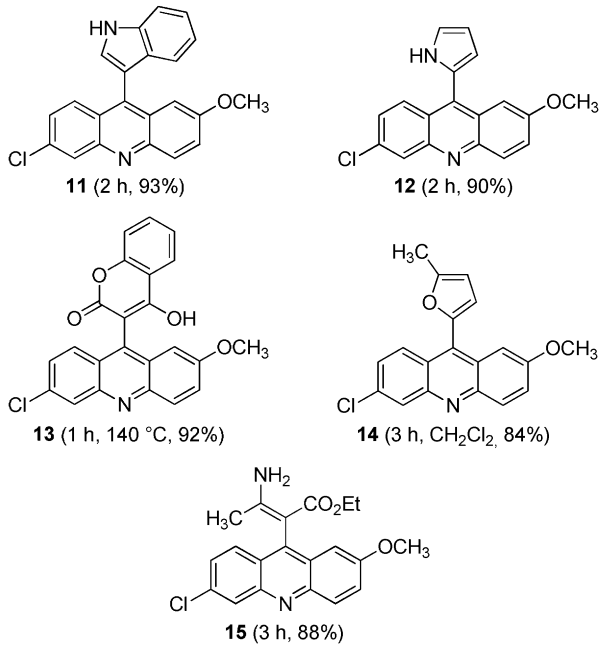


Figure 3. C–C bond forming reactions at the acridine C-9 position.

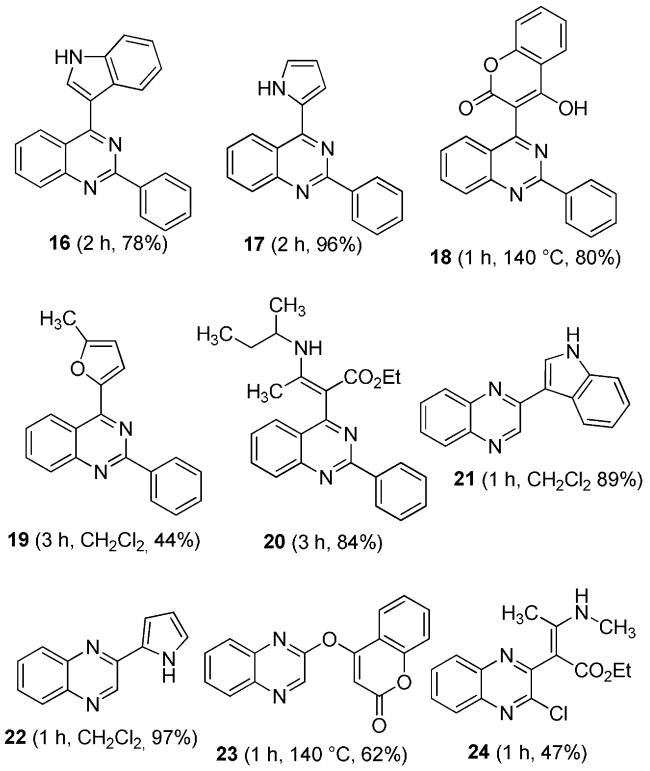
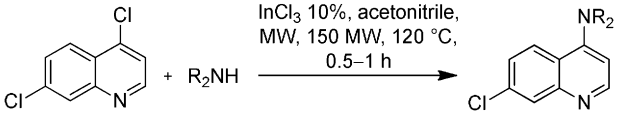


Figure 4. C–C bond forming reactions at the quinazoline C-4 and quinoxaline C-2 positions.

ingly, the reaction between 4-hydroxycoumarin and 2-chloroquinoxaline afforded the O-arylation product **23**, while its treatment with ethyl 3-methylaminocrotonate generated a C–C bond at the quinoxaline C-3 position to give **24**. Some of the reactions (i.e., those leading to **19**, **23** and **24**) gave comparatively low yields, which was due to the recovery of unreacted starting material. These results could not be improved by increasing the reaction times.



Scheme 3. C–N coupling reactions of 4,7-dichloroquinoline.

The regioselective formation of compound **24** is noteworthy in that it must involve an addition to the position α to the halogen atom, followed by air oxidation of the initial adduct, instead of the usual addition to the position *ipso* to the halogen followed by elimination of hydrogen halide. This behaviour is relatively common in reactions involving hindered C-nucleophiles and ambivalent, monohalogenated electrophiles such as haloquinones,[23] and is probably due to steric effects.

At this stage, and spurred by the huge pharmaceutical importance of aminoheterocycles, we decided to study the extension of our method to amination reactions. When tested on the 4,7-dichloroquinoline substrate, it turned out to be extremely efficient for aromatic, primary aliphatic and secondary aliphatic amines, and was also useful for the N-arylation of benzimidazole (Scheme 3 and Figure 5). Furthermore, compound isolation required simple filtration and no further purification was needed, and hence the use of volatile organic solvents in extraction and chromatographic purification steps was unnecessary.

Microwave irradiation was essential for the success of the method, as shown by the comparison of the conditions required and the yields obtained for the synthesis of **25** and **26** under reflux.

This new method was also compared with our recently reported protocol involving microwave irradiation of the starting materials in the presence of two equivalents of phenol,[24] which overcame many drawbacks of the application of conventional procedures.[25] Reaction times and yields were similar but, since the new protocol avoided the use of the toxic and corrosive phenol, it can be regarded as meeting more stringent green chemistry requirements. Furthermore, for the first time, a Lewis acid was shown to be an effective catalyst for this type of amination reactions.

The coupling of 6,9-dichloro-2-methoxyacridine with representative amines was also carried out, affording compounds **30**–**34** in excellent yields as coloured precipitates that, after filtration, did not require further purification. As in the case of quinoline, the reaction tolerated well the use of different structural

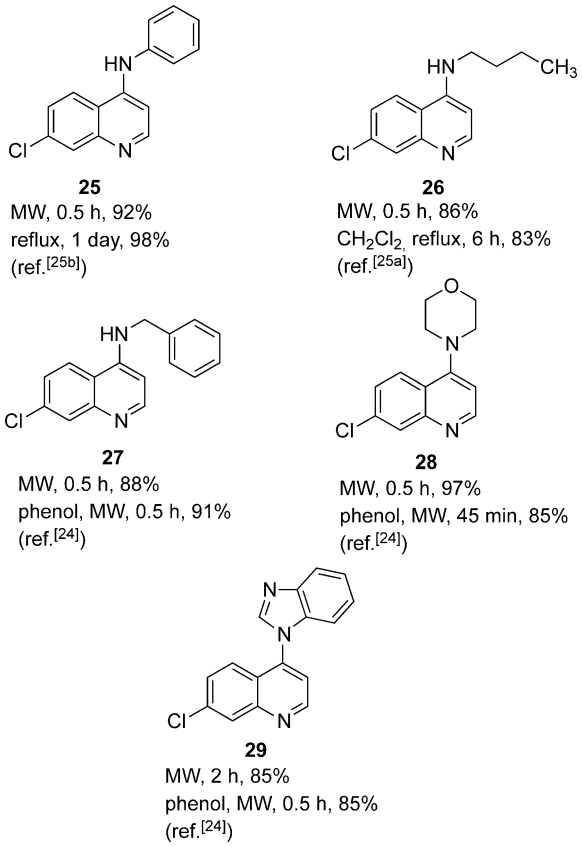


Figure 5. C–N bond forming reactions at the quinoline C-4 position.

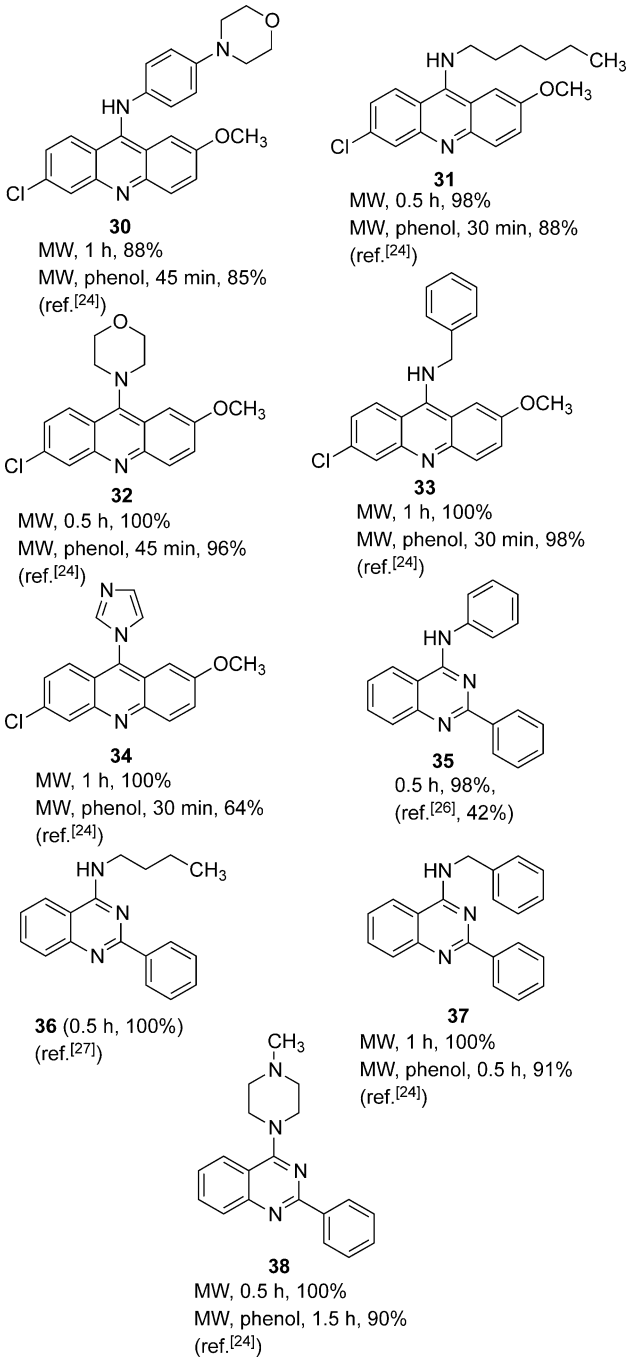


Figure 6. C–N bond forming reactions at the acridine and quinazoline C-9 and C-4 positions, respectively.

types of amines. Similar results were obtained for quinazoline derivatives **35**–**38** (Figure 6). A comparison with the results obtained for these compounds employing our first-generation method revealed similar yields, although the previously mentioned advantages associated to the avoidance of phenol are noteworthy. A considerable improvement of the yield of the imidazolyl derivative **34** was observed in comparison with our previous method, and comparison with previous literature methods revealed our protocol to give improved yields in the cases when a comparison was possible,[26] avoiding the use of phenol or bulky phosphonium ligands.[27]

In order to confirm the generality of our new protocol, we briefly examined the reactivity towards amines of several additional halogenated nitrogen heterocycles, including 2-chloroquinaxoline,[28] 4-chloropurine,[29] 2-chlorobenzimidazole[11b,30] and 2-chloropyridine[12f] to provide compounds **39**–**53** in excellent yields (Figure 7) for which no general method of synthesis was available.

As final step, we applied our method to the synthesis of several representative antimalarial drugs that are currently in clinical use,[31] including amodiaquine, chloroquine and mepacrine (quinacrine). Thus, the reaction under our standard conditions between 4,7-dichloroquinoline and the commercially available 5-diethylaminopentan-2-amine afforded chloroquine (**54**), while the use of 4-amino-2-(diethylaminomethyl)-*ortho*-cresol furnished amodiaquine (**55**) in 73% and 71% yields, respectively (Scheme 4). Similarly, mepacrine (**56**) was prepared in good yield (75%) by reaction between 6,9-dichloro-2-methoxyacridine and 5-diethylaminopentan-2-amine (Scheme 5). The last

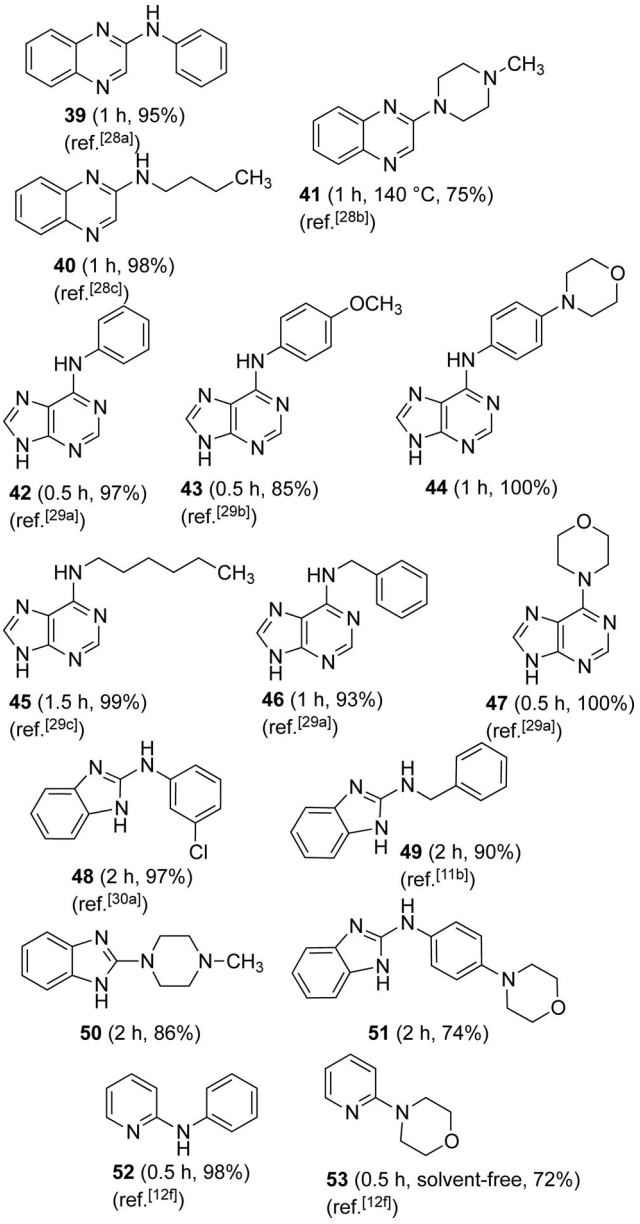
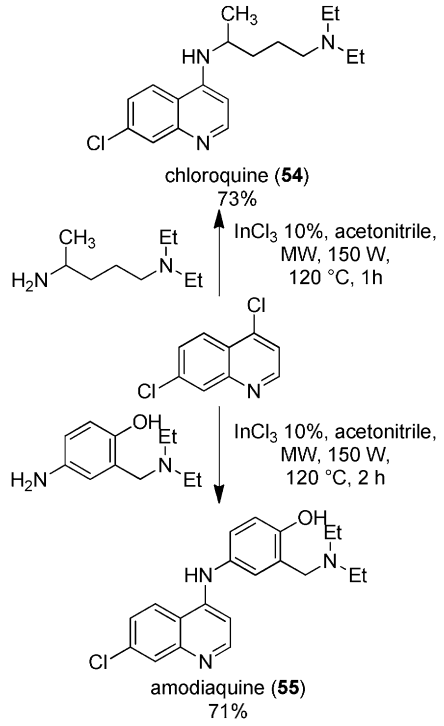
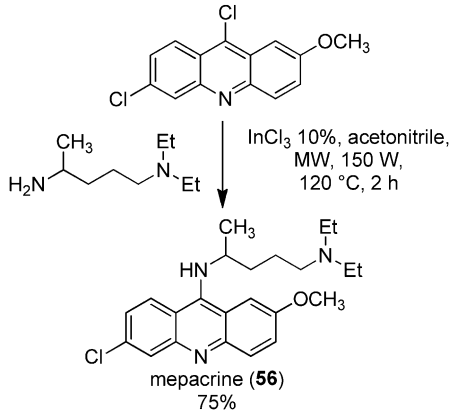


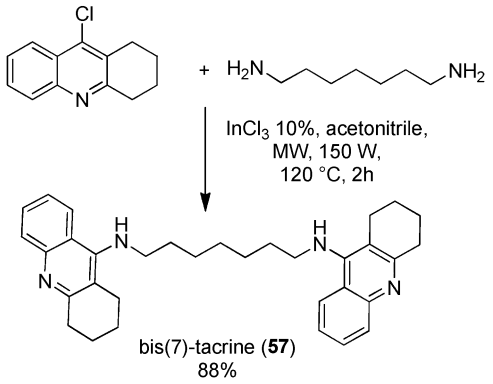
Figure 7. C–N bond forming reactions at the quinoxaline C-2, purine C-6, benzimidazole C-2 and pyridine C-2 positions.



Scheme 4. Synthesis of the antimalarial drugs chloroquine and amodiaquine.



Scheme 5. Synthesis of the antimalarial drug mepacrine.



Scheme 6. Synthesis of the anti-Alzheimer drug candidate bis(7)-tacrine.

proof of the versatility of our protocol came from an example of a double amination, i.e., the synthesis of bis(7)-tacrine (**57**), an anti-Alzheimer drug candidate currently in clinical development.[32] To this end, 9-chloro-1,2,3,4-tetrahydroacridine was treated with half an equivalent of 1,7-heptanediamine in the presence of $InCl_3$ under our usual microwave conditions to give the target compound (**57**) in 88% yield (Scheme 6).

To the best of our knowledge, this is the first example of the use of a Lewis acid for this purpose, and represents an improvement of our recently reported a protocol for the S_NAr displacement of halogen atoms by amines in π-deficient heterocyclic substrates

in the presence of two equivalents of phenol and under focused microwave irradiation. While these conditions overcame many drawbacks found using conventional procedures, only three heterocyclic nuclei were explored, namely acridine, quinoline and quinazoline. In addition, the toxicity and corrosive nature of phenol detracted from the user-friendliness and sustainability of the method.

Conclusions

In summary, we have developed a simple, general, one-pot coupling reaction that allows the rapid and fully regioselective generation of both aromatic C–C and C–N bonds on a variety of pharmaceutically relevant nitrogen heterocycles. The process is highly affordable, as it requires only an equimolecular mixture of simple starting materials and a catalytic amount of the relatively inexpensive Lewis acid $InCl_3$. Furthermore, in most cases work-up required only a simple filtration and hence no organic solvents were needed for extraction and chromatographic purification steps. Some noteworthy features of the method include: (a) the high yields and relatively short reaction times compared with those needed under conventional conditions; (b) the first use of a Lewis acid as a catalyst in heteroarylation, vinylation and amination reactions on π-deficient heterocyclic substrates; (c) the confirmation of the generality of the method by its application to target-oriented synthesis.

Experimental Section

General Information

All reagents (Aldrich, Fluka, SDS, Probus) and solvents (SDS), were of commercial quality and were used as received. Reactions were monitored by thin layer chromatography, on aluminium plates coated with silica gel with fluorescent indicator (SDS CCM221254). Separations by flash chromatography were performed on silica gel (SDS 60 ACC 40e63 mm) or neutral alumina (Merck S22). Melting points were measured on a Reichert 723 hot stage microscope, and are uncorrected. Infrared spectra were recorded on a Nicolet IR 200 FT-IR spectrophotometer, with all compounds examined as KBr pellets or as thin films on NaCl disks. NMR spectra were obtained on a Bruker Avance 250 spectrometer operating at 250 MHz for ^1H and 63 MHz for ^{13}C (CAI de Resonancia Magnetica Nuclear, Universidad Complutense). Combustion elemental analyses were determined by the CAI de Microanalisis Elemental, Universidad Complutense.

General Synthetic Method

The suitable starting heterocycle (0.5 mmol), the corresponding nucleophile (1 equiv.) and 10% mol of $InCl_3$ were charged in a pressure-tight microwave tube containing 2 mL of acetonitrile (or 2 mL of CH_2Cl_2 in the reactions starting from 2-methylfuran) and a stirring bar. The reaction mixture was submitted to microwave irradiation for 30 min to 3 h at 120 °C (except 4-hydroxycoumarin at 140 °C), with an irradiation power of 150 W, using a CEM Discover SP focused microwave reactor. If a precipitate was formed, simple filtration gave the final products; otherwise, the mixture was dissolved in CH_2Cl_2, washed with H_2O, dried, and evaporated. In the latter case, analytically pure compounds were obtained by flash chromatography on silica gel. Characterization data for compounds **1--24** and **54--57** are given below. For the rest of the data, see the Supporting Information.

7-Chloro-4-(1*H*-indol-3-yl)quinolinium chloride (1): yellow solid; mp 260 °C; ^1H NMR (250 MHz, DMSO): δ = 12.56 (br s, 1H), 9.26 (d, J = 5.7 Hz, 1H), 8.64 (d, J = 9.2 Hz, 1H), 8.55 (d, J = 1.8 Hz, 1H), 8.31 (d, J = 2.7 Hz, 1H), 8.18 (d, J = 5.7 Hz, 1H), 8.02 (dd, J = 9.1, 1.9 Hz, 1H), 7.88 (d, J = 7.7 Hz, 1H), 7.75 (d, J = 7.9 Hz, 1H), 7.47–7.33 (m, 2H); ^{13}C NMR (63 MHz, MeOD): δ = 152.7, 147.4, 144.1, 140.6, 139.3, 131.3 (2C), 130.6, 127.5, 126.9, 124.9, 123.8, 123.1, 122.0, 120.5, 114.0, 113.2; IR (KBr disk): ν = 3291, 3088, 1626, 1591, 1517, 1421, 1234, 830, 739 cm^{-1}; elemental analysis calcd. (%) for $C_{17}H_{12}Cl_2N_2$: C 64.78, H 3.84, N 8.89; found: C 64.61, H 3.64, N 8.85.

(*Z*)-Ethyl 3-amino-2-(7-chloroquinolin-4-yl)but-2-enoate (2): white solid; mp 157 °C; ^1H NMR (250 MHz, $CDCl_3$): δ = 8.89 (d, J = 4.5, 1H), 8.15 (d, J = 2.0, 1H), 7.83 (d, J = 8.9, 1H), 7.47 (dd, J = 9.0, 2.1 Hz, 1H), 7.25 (d, J = 4.5, 1H), 4.08–3.95 (m, 2H), 1.66 (s, 3H), 0.99 (t, J = 7.1 Hz, 3H); ^{13}C NMR (63 MHz, $CDCl_3$): δ = 169.2, 159.3, 151.5, 149.3, 146.2, 135.3, 128.8, 128.4, 127.8, 127.6, 125.1, 93.3, 59.7, 21.8, 14.7; IR (NaCl): ν = 3416, 3312, 2979, 2925, 1664, 1614, 1251, 1101 cm^{-1}; elemental analysis calcd. (%) for $C_{15}H_{15}ClN_2O_2$: C 61.97, H 5.20, N 9.64; found: C 61.32, H 5.32, N 9.15.

7-Chloro-4-(4-hydroxy-2-oxo-2*H*-chromen-3-yl)quinolinium chloride (3): yellow solid; mp 258 °C; ^1H NMR (250 MHz, DMSO): δ = 9.20 (d, J = 5.1 Hz, 1H), 8.34 (s, 1H), 8.08 (d, J = 8.7 Hz, 2H), 7.92 (d, J = 5.1 Hz, 1H), 7.78–7.71 (m, 2H), 7.50–7.40 (m, 2H); ^{13}C NMR (63 MHz, DMSO): δ = 164.5, 161.4, 153.6, 149.2, 147.0, 141.4, 137.8, 133.6, 129.8, 129.5, 127.3, 125.8, 124.9, 124.5, 122.4, 117.2, 116.9, 100.4; IR (KBr disk): ν = 2581, 1732, 1598, 1494, 1381, 1199, 1848, 961 cm^{-1}; elemental analysis calcd. (%) for $C_{18}H_{11}Cl_2NO_3$: C 60.02, H 3.08, N 3.89; found: C 59.49, H 3.11, N 4.00.

7-Chloro-4-(5-methylfuran-2-yl)quinoline (4): red solid; mp 71 °C; ^1H NMR (250 MHz, MeOD): δ = 8.77 (d, J = 5.0 Hz, 1H), 8.67 (d, J = 9.2 Hz, 1H), 7.96 (s, 1H), 7.81 (d, J = 5.1 Hz, 1H), 7.64 (dd, J = 9.0, 1.0 Hz, 1H), 7.30 (d, J = 3.3 Hz, 1H), 6.34 (d, J = 2.8 Hz, 1H), 2.49 (d, J = 37.6 Hz, 3H); ^{13}C NMR (63 MHz, MeOD): δ = 159.4, 150.0, 149.6, 146.9, 141.2, 139.2, 130.5, 130.0, 126.0, 123.9, 119.7, 118.8, 111.4, 14.3; IR (NaCl): ν = 3066, 1619, 1506, 1207, 1089 cm^{-1}; elemental analysis calcd. (%) for $C_{14}H_{10}ClNO$: C 69.00, H 4.14, N 5.75; found: C 68.82, H 4.05, N 5.52.

7-Chloro-4-(1*H*-pyrrol-2-yl)quinolinium chloride (5): Yellow solid; mp 179 °C; ^1H NMR (250 MHz, $CDCl_3$): δ = 9.01 (br s, 1H), 8.83 (d, J = 4.6 Hz, 1H), 8.35 (d, J = 9.1 Hz, 1H), 8.11 (d, J = 2.1 Hz, 1H), 7.51 (dd, J = 9.1, 2.2 Hz, 1H), 7.35 (d, J = 4.6 Hz, 1H), 7.14–7.11 (m, 1H), 6.75–6.72 (m, 1H), 6.51–6.48 (m, 1H); ^{13}C NMR (63 MHz, $CDCl_3$): δ = 151.2, 149.7, 139.9, 135.9, 129.0, 128.1, 127.9, 127.7, 124.5,

121.5, 119.2, 112.8, 111.1 ppm; IR (NaCl): ν = 1583, 1498, 1431, 1370, 1257, 1136, 1041, 916 cm^{-1}; elemental analysis calcd. (%) for $C_{13}H_{10}Cl_2N_2$: C 58.89, H 3.80, N 10.57; found: C 58.49, H 4.10, N 10.48.

(*Z*)-Ethyl 2-(7-chloroquinolin-4-yl)-3-(methylamino)but-2-enoate (6): pale brown solid; mp 99 °C; ^{1}H NMR (250 MHz, $CDCl_3$): δ = 9.60 (br s, 1H), 8.78 (d, J = 4.4 Hz, 1H), 8.03 (d, J = 2.1 Hz, 1H), 7.73 (d, J = 8.9 Hz, 1H), 7.35 (dd, J = 9.0, 2.1 Hz, 1H), 7.11 (d, J = 4.4 Hz, 1H), 3.95–3.81 (m, 2H), 2.94 (d, J = 5.2 Hz, 3H), 1.56 (s, 3H), 0.88 (t, J = 7.1 Hz, 3H); ^{13}C NMR (63 MHz, $CDCl_3$): δ = 169.7, 162.5, 151.7, 149.4, 146.7, 135.1, 128.9, 128.8, 127.9, 127.4, 125.5, 91.1, 59.4, 30.5, 17.0, 14.8; IR (NaCl): ν = 3263, 2974, 2930, 1647, 1597, 1265, 1231, 1061 cm^{-1}; Eelemental analysis calcd. (%) for $C_{16}H_{17}ClN_2O_2$: C 63.05, H 5.62, N 9.19; found: C 62.95, H 5.44, N 9.03.

(*Z*)-Ethyl 3-(butylamino)-2-(7-chloroquinolin-4-yl)but-2-enoate (7): pale brown solid; mp 102 °C; ^{1}H NMR (250 MHz, $CDCl_3$): δ = 9.75 (br t, J = 5.0 Hz, 1H), 8.88 (d, J = 4.4 Hz, 1H), 8.12 (d, J = 2.1 Hz, 1H), 7.83 (d, J = 8.9 Hz, 1H), 7.44 (dd, J = 8.9, 2.1 Hz, 1H), 7.21 (d, J = 4.4 Hz, 1H), 4.07–3.89 (m, 2H), 3.37–3.29 (m, 2H), 1.78–1.66 (m, 2H), 1.65 (s, 3H), 1.58–1.43 (m, 2H), 1.04–0.94 (m, 6H); ^{13}C NMR (63 MHz, $CDCl_3$): δ = 169.6, 161.6, 151.7, 149.5, 146.8, 135.1, 128.9, 128.8, 128.0, 127.4, 125.5, 90.8, 59.3, 43.7, 32.6, 20.6, 17.2, 14.8, 14.3; IR (NaCl): ν = 3251, 2970, 2932, 1645, 1594, 1264, 1228, 877 cm^{-1}; elemental analysis calcd. (%) for $C_{19}H_{23}ClN_2O_2$: C 65.79, H 6.68, N 8.08; found: C 65.29, H 6.55, N 8.12.

(*Z*)-Ethyl 3-(*sec*-butylamino)-2-(7-chloroquinolin-4-yl)but-2-enoate (8): white solid; mp 115 °C; ^{1}H NMR (250 MHz, $CDCl_3$): δ = 9.66 (br d, J = 8.9 Hz, 1H), 8.78 (d, J = 4.4 Hz, 1H), 8.02 (d, J = 2.1 Hz, 1H), 7.73 (dd, J = 8.9, 4.9 Hz, 1H), 7.35 (dd, J = 8.9, 2.1 Hz, 1H), 7.13 (dd, J = 4.4, 1.5 Hz, 1H), 3.95–3.81 (m, 2H), 3.55–3.39 (m, 1H), 1.59–1.52 (m, 2H), 1.56 (s, 3H), 1.20 (dd, J = 6.4, 2.0 Hz, 3H), 0.98–0.84 (m, 6H); ^{13}C NMR (63 MHz, $CDCl_3$): δ = 169.6, 160.8, 151.8, 149.5, 146.9, 135.1, 128.9, 128.0, 127.9, 127.4, 125.6, 90.5, 59.3, 50.9, 31.4, 22.2, 17.2, 14.8, 11.0; IR (NaCl): ν = 3250, 2971, 2927, 1645, 1594, 1561, 1536, 1335, 1241, 710 cm^{-1}; elemental analysis calcd. (%) for $C_{19}H_{23}ClN_2O_2$: C 65.79, H 6.68, N 8.08; found: C 65.73; H 6.58; N 8.13.

(*Z*)-Ethyl 2-(7-chloroquinolin-4-yl)-3-(furan-2-ylmethylamino)but-2-enoate (9): yellow oil; ^{1}H NMR (250 MHz, $CDCl_3$): δ = 10.03 (br t, J = 5.6 Hz, 1H), 8.89 (d, J = 4.6 Hz, 1H), 8.23 (d, J = 2.0 Hz, 1H), 7.85 (d, J = 9.0 Hz, 1H), 7.49 (dd, J = 9.0, 2.1 Hz, 1H), 7.44 (dd, J = 1.8, 0.8 Hz, 1H), 7.28 (d, J = 4.6 Hz, 1H), 6.40 (dd, J = 3.2, 1.9 Hz, 1H), 6.31 (dd, J = 3.2, 0.8 Hz, 1H), 4.52 (d, J = 5.9 Hz, 2H), 4.04–3.94 (m, 2H), 1.75 (s, 3H), 0.97 (t, J = 7.1 Hz, 3H); ^{13}C NMR (63 MHz, $CDCl_3$): δ = 167.9, 159.6, 150.1, 149.2, 146.8, 146.4, 141.6, 134.5, 127.3, 126.6, 126.5 (2H), 123.9, 109.5, 106.4, 91.0, 58.2, 39.5, 15.8, 13.3; IR (NaCl): ν = 3255, 2980, 2930, 1651, 1583, 1444, 1262, 1231, 1095, 1071, 1016 cm^{-1}; elemental analysis calcd. (%) for $C_{20}H_{19}ClN_2O_3$: C 64.78, H 5.16, N 7.55; found: C 64.55, H 4.99, N 7.23.

(*Z*)-Ethyl 3-(benzylamino)-2-(7-chloroquinolin-4-yl)but-2-enoate (10): yellow oil; ^{1}H NMR (250 MHz, $CDCl_3$): δ = 10.13 (br t, J = 5.9 Hz, 1H), 8.88 (d, J = 4.4 Hz, 1H), 8.13 (d, J = 2.1 Hz, 1H), 7.84 (d, J = 8.9 Hz, 1H), 7.48–7.34 (m, 6H), 7.23 (d, J = 4.4 Hz, 1H), 4.56 (d, J = 6.1 Hz, 2H), 4.07–3.93 (m, 2H), 1.66 (s, 3H), 0.98 (t, J = 7.1 Hz, 3H); ^{13}C NMR (63 MHz, $CDCl_3$): δ = 169.7, 161.5, 151.7, 149.4, 146.5, 138.6, 135.2, 129.4 (2C), 128.9, 128.7, 128.0, 127.8, 127.5, 127.3 (2C), 125.4, 92.2, 59.5, 47.7, 17.3, 14.7; IR (NaCl): ν = 3237, 2977, 2923, 1651, 1607, 1260, 1230 cm^{-1}; elemental analysis calcd. (%) for $C_{22}H_{21}ClN_2O_2$: C 69.38, H 5.56, N 7.36; found: C 69.01, H 5.34, N 7.24.

6-Chloro-9-(1*H*-indol-3-yl)-2-methoxyacridinium chloride (11): yellow solid; mp 223 °C; ^{1}H NMR (250 MHz, $CDCl_3$): δ = 8.79 (br s, 1H), 8.28 (d, J = 1.8 Hz, 1H), 8.19 (d, J = 9.4 Hz, 1H), 7.89 (d, J = 9.3 Hz, 1H), 7.63 (d, J = 8.2 Hz, 1H), 7.51 (dd, J = 7.7, 2.4 Hz, 2H), 7.39–7.31 (m, 2H), 7.23–7.12 (m, 3H), 3.69 (s, 3H); ^{13}C NMR (63 MHz, $CDCl_3$): δ = 157.5, 147.6, 146.9, 139.5, 136.5, 135.3, 131.3, 128.9, 128.2, 128.2, 127.6, 127.1, 126.1, 125.7, 125.3, 123.4, 121.1, 120.7, 112.0, 111.4, 103.2, 55.8; IR (NaCl): ν = 1628, 1563, 1535, 1466, 1419, 1209, 701 cm^{-1}; elemental analysis calcd- (%) for $C_{22}H_{16}Cl_2N_2O$: C 66.85, H 4.08, N 7.09; found: C 66.72, H 4.15, N 7.24.

6-Chloro-2-methoxy-9-(1*H*-pyrrol-2-yl)acridinium chloride (12): Yellow solid; mp 236 °C; ^{1}H NMR (250 MHz, $CDCl_3$): δ = 9.40 (br s, 1H), 8.06 (d, J = 2.0 Hz, 1H), 7.94 (d, J = 9.4 Hz, 1H), 7.82 (d, J = 9.4 Hz, 1H), 7.35–7.27 (m, 3H), 7.05 (d, J = 2.1 Hz, 1H), 6.60–6.57 (m, 2H), 3.84 (s, 3H); ^{13}C NMR (63 MHz, acetone-d_6): δ = 158.7, 148.6, 148.1, 138.7, 135.3, 132.6, 130.1, 129.1, 127.9, 127.8, 126.7, 125.6, 121.6, 121.4, 113.5, 110.3, 103.8, 56.2; IR (NaCl): ν = 1630, 1473, 1232, 807 cm^{-1}; elemental analysis calcd. (%) for $C_{18}H_{14}Cl_2N_2O$: C 62.62, H 4.09, N 8.11; found: C 62.23, H 4.25, N 8.21.

6-Chloro-9-(4-hydroxy-2-oxo-2*H*-chromen-3-yl)-2-methoxyacridinium chloride (13): orange solid; mp > 300 °C; ^{1}H NMR (250 MHz, DMSO): δ = 8.43 (d, J = 2.0 Hz, 1H), 8.34 (d, J = 9.4 Hz, 1H), 8.14 (d, J = 9.3 Hz, 1H), 8.08 (dd, J = 7.9, 1.4 Hz, 1H), 7.85–7.76 (m, 2H), 7.67 (dd, J = 9.3, 2.1 Hz, 1H), 7.58 (dd, J = 8.3, 0.7 Hz, 1H), 7.51–7.44 (m, 1H), 7.28 (d, J = 2.6 Hz, 1H), 3.85 (s, 3H); ^{13}C NMR (63 MHz, DMSO): δ = 164.2, 161.2, 158.2, 154.0, 139.4, 137.0, 133.5, 129.3, 129.1, 129.0, 128.3, 128.1, 127.3, 127.3, 125.2, 124.6, 124.5, 123.9, 117.0, 116.9, 103.0, 98.5, 56.4; IR (KBr disk): ν = 1696, 1606, 1228, 1043, 951, 761 cm^{-1}; elemental analysis calcd. (%) for $C_{23}H_{15}Cl_2NO_4$: C 62.74, H 3.43, N 3.18; found: C 62.31, H 3.39, N 3.45.

6-Chloro-2-methoxy-9-(5-methylfuran-2-yl)acridinium chloride (14): brown solid; mp 171 °C; ^{1}H NMR (250 MHz, MeOD): δ = 8.64 (d, J = 9.5 Hz, 1H), 8.26–8.21 (m, 2H), 7.99–7.84 (m, 3H), 7.47 (s, 1H), 6.72 (s, 1H), 4.05 (s, 3H), 2.66 (s, 3H); ^{13}C NMR (63 MHz, MeOD): δ = 159.6, 145.0, 143.4, 142.0, 139.8, 131.8, 130.3, 129.4, 125.6, 125.1, 123.1, 123.1, 122.6, 121.7, 118.8, 110.4, 104.4, 55.6, 13.0; IR (KBr disk): ν = 3120, 1626, 1526, 1453, 1240 cm^{-1}; elemental analysis calcd. (%) for $C_{19}H_{15}Cl_2NO_2$: C 63.35, H 4.20, N 3.89; found: C 63.01, H 3.97, N 3.63.

(*Z*)-9-(3-Amino-1-ethoxy-1-oxobut-2-en-2-yl)-6-chloro-2-methoxyacridinium (15): orange solid; mp 245 °C; ^{1}H NMR (250 MHz, MeOD): δ = 8.34–8.24 (m, 3H), 7.96 (dd, J = 9.5, 2.6 Hz, 1H), 7.83 (d, J = 9.5 Hz, 1H), 7.47 (d, J = 2.5 Hz, 1H), 4.02 (s, 3H), 4.04–3.94 (m, 2H), 1.58 (s, 3H), 0.88 (t, J = 7.1 Hz, 3H); ^{13}C NMR (63 MHz, DMSO): δ = 167.8, 161.9, 157.5, 156.4, 135.8, 135.4, 135.1, 132.8, 128.9, 128.4, 127.5, 127.5, 127.4, 125.9, 102.3, 86.5, 58.4, 55.9, 20.4, 14.7; IR (KBr disk): ν = 3348, 3240, 3164, 1660, 1628, 1426, 1239,

1017 cm^{-1}; elemental analysis calcd. (%) for $C_{20}H_{19}ClN_2O_3$: C 58.98, H 4.95, N 6.88; found: C 58.78, H 4.96, N 7.06.

4-(1*H*-Indol-3-yl)-2-phenylquinazolin-1-ium chloride (16): pale yellow solid; mp 244 °C; ^{1}H NMR (250 MHz, $CDCl_3$): δ = 8.77 (dd, J = 8.0, 1.7 Hz, 2H), 8.42 (d, J = 6.9 Hz, 2H), 8.19 (d, J = 8.4 Hz, 1H), 7.95–7.88 (m, 2H), 7.63–7.54 (m, 5H), 7.41–7.37 (m, 2H); ^{13}C NMR (63 MHz, $CDCl_3$): δ(= 164.0, 160.8, 152.3, 139.0, 137.1, 136.9, 133.7, 130.8, 129.3, 129.0 (2H), 129.0 (2H), 127.3, 127.1, 127.0, 123.7, 122.3, 122.1, 121.9, 114.8, 111.9; IR (NaCl): ν = 1524, 1483, 1456, 1438, 1341, 1240, 745, 706 cm^{-1}; elemental analysis calcd. (%) for $C_{22}H_{16}ClN_3$: C 73.84, H 4.51, N 11.74 found: C 73.97, H 4.76, N 11.71.

2-Phenyl-4-(1*H*-pyrrol-2-yl)quinazolin-1-ium chloride (17): brown solid; mp 197 °C; ^{1}H NMR (250 MHz, MeOD): δ = 8.54–8.46 (m, 3H), 7.90–7.79 (m, 2H), 7.61–7.55 (m, 1H), 7.48–7.44 (m, 3H), 7.28 (d, J = 3.9 Hz, 1H), 7.20–7.19 (m, 1H), 6.39 (dd, J = 3.6, 2.5 Hz, 1H); ^{13}C NMR (63 MHz, MeOD): δ = 160.4, 160.2, 150.1, 137.6, 136.2, 133.1, 130.4 (2C), 130.3 (2C), 130.2, 129.6, 128.3, 127.1, 124.4, 120.8, 120.4, 113.9; IR (NaCl): ν = 3440, 2923, 1561,1488, 1431, 1338, 760 cm^{-1}; elemental analysis calcd. (%) for $C_{18}H_{14}ClN_3$: C 70.24, H 4.58, N 13.65; found: C 70.63, H 4.88, N 13.62.

4-Hydroxy-3-(2-phenylquinazolin-4-yl)-1*H*-isochromen-1-one (18): yellow solid; mp 276 °C; ^{1}H NMR (250 MHz, DMSO): δ = 8.57–8.53 (m, 2H), 8.17–8.02 (m, 4H), 7.82–7.76 (m, 1H), 7.70–7.45 (m, 6H); ^{13}C NMR (63 MHz, MeOD): δ = 164.6, 162.9, 161.2, 158.7, 153.3, 150.7, 137.0, 134.9, 133.5, 131.0, 128.9 (2C), 128.4, 128.2 (2C), 127.7, 127.2, 124.4 (2C), 123.2, 116.6, 116.6, 101.5; IR (KBr disk): ν = 1704, 1609, 1558, 1470, 1381, 1356, 756 cm^{-1}; elemental analysis calcd. (%) for $C_{23}H_{14}N_2O_3$: C 75.40, H 3.85, N 7.65; found: C 75.28, H 3.79, N 7.78.

4-(5-Methylfuran-2-yl)-2-phenylquinazoline (19): yellow solid; mp 100 °C; ^{1}H NMR (250 MHz, $CDCl_3$): δ = 8.95 (dd, J = 8.5, 0.7 Hz, 1H), 8.69 (dd, J = 7.8, 1.9 Hz, 2H), 8.10 (d, J = 7.9 Hz, 1H), 7.92–7.85 (m, 1H), 7.68–7.52 (m, 5H), 6.35 (dd, J = 3.4, 0.9 Hz, 1H), 2.59 (s, 3H); ^{13}C NMR (63 MHz, $CDCl_3$): δ = 160.5, 157.0, 155.6, 153.1, 152.9, 138.7, 133.8, 130.8, 129.5, 128.9 (2C), 128.9 (2C), 127.5, 127.2, 119.9, 118.0, 109.5, 14.8; IR (NaCl): ν = 3060, 1563, 1545, 1515, 1334, 764, 706 cm^{-1}; elemental analysis calcd. (%) for $C_{19}H_{14}N_2O$: C 79.70, H 4.93, N 9.78; found: C 79.76, H 4.54, N 9.42.

(*Z*)-Ethyl 3-(*sec*-butylamino)-2-(2-phenylquinazolin-4-yl)but-2-enoate (20): pale yellow solid; mp 124 °C; ^{1}H NMR (250 MHz, $CDCl_3$): δ = 9.93 (br d, J = 8.6 Hz, 1H), 8.65–8.61 (m, 2H), 8.09 (d, J = 8.4 Hz, 1H), 7.97 (d, J = 7.7 Hz, 1H), 7.87–7.81 (m, 1H), 7.59–7.47 (m, 4H), 4.05–3.94 (m, 2H), 3.73–3.57 (m, 1H), 1.94 (s, 3H), 1.74–1.63 (m, 2H), 1.33 (d, J = 6.4 Hz, 3H), 1.06 (t, J = 7.4 Hz, 3H), 0.92 (t, J = 7.1 Hz, 3H); ^{13}C NMR (63 MHz, $CDCl_3$): δ = 169.8, 169.2, 162.6, 160.9, 151.6, 139.1, 133.6, 130.6, 129.1, 129.0 (2C), 128.9 (2C), 127.8, 126.6, 125.7, 92.8, 59.2, 51.0, 31.2, 22.1, 17.1, 14.7, 10.9; IR (KBr disk): ν = 3246, 3147, 3064, 2974, 2923, 1646, 1596, 1254, 710 cm^{-1}; elemental analysis calcd. (%) for $C_{24}H_{27}N_3O_2$: C 74.01, H 6.99, N 10.79; found: C 73.77, H 6.86, N 10.65.

2-(1*H*-Indol-3-yl)quinoxalin-1-ium chloride (21): red solid; mp 206 °C; ^{1}H NMR (250 MHz, DMSO): δ = 12.00 (br s, 1H), 9.52 (s, 1H), 8.82–8.79 (m, 1H), 8.65–8.64 (m, 1H), 8.10 (d, J = 8.2 Hz, 1H), 8.02 (d, J = 8.1 Hz, 1H), 7.84–7.77 (m, 1H), 7.72–7.66 (m, 1H), 7.55–7.51 (m, 1H), 7.28–7.25 (m, 2H); ^{13}C NMR (63 MHz, DMSO): δ = 151.2, 144.8, 142.1, 139.5, 137.5, 130.5, 129.6, 128.9, 128.7, 128.2, 125.8, 123.1, 122.7, 121.3, 113.1, 112.5; IR (KBr): ν = 3255, 1553, 1446, 1170, 1133 cm^{-1}; elemental analysis calcd. (%) for $C_{16}H_{12}ClN_3$: C 68.21, H 4.29, N 14.91; found: C 67.96, H 4.03, N 14.42.

2-(1*H*-Pyrrol-2-yl)quinoxalin-1-ium chloride (22): yellow solid; mp 150 °C; ^{1}H NMR (250 MHz, $CDCl_3$): δ = 9.80 (br s, 1H), 9.16 (s, 1H), 8.07–7.96 (m, 2H), 7.77–7.63 (m, 2H), 7.10–7.06 (m, 2H), 6.44–6.425 (m, 1H); ^{13}C NMR (63 MHz, $CDCl_3$): δ = 145.4, 143.1, 142.4, 141.2, 130.7, 129.9, 129.6, 128.8, 128.6, 122.7, 111.5, 110.9; IR (NaCl): ν = 3189, 1568, 1430, 1128, 1115, 753, 717 cm^{-1}; elemental analysis calcd. (%) for: $C_{12}H_{10}ClN_3$: C 62.21, H 4.35, N 18.14; found: C 62.45, H 4.52, N 18.34.

4-(Quinoxalin-2-yloxy)-2*H*-chromen-2-one (23): yellow solid; mp 125 °C; ^{1}H NMR (250 MHz, $CDCl_3$): δ = 8.89 (s, 1H), 8.23–8.19 (m, 1H), 8.01–7.98 (m, 2H), 7.89–7.79 (m, 2H), 7.70–7.65 (m, 1H), 7.48–7.37 (m, 2H), 6.72 (s, 1H); ^{13}C NMR (63 MHz, $CDCl_3$): δ = 162.5, 161.6, 154.4, 154.1, 141.2, 139.9, 139.2, 133.4, 131.9, 129.9, 129.7, 128.6, 124.8, 123.5, 117.5, 115.9, 100.8; IR (NaCl): ν = 2923, 1724, 1384, 1301, 1216, 1178, 762 cm^{-1}; elemental analysis calcd. (%) for $C_{17}H_{10}N_2O_3$: C 70.34, H 3.47, N 9.65; found: C 70.11, H 3.22, N 9.45.

(*Z*)-Ethyl 2-(3-chloroquinoxalin-2-yl)-3-(methylamino)-but-2-enoate (24): yellow solid; mp 115 °C; ^{1}H NMR (250 MHz, $CDCl_3$): δ = 8.38–8.34 (m, 1H), 8.14–8.10 (m, 1H), 7.74–7.70 (m, 2H), 4.55 (q, J = 7.1 Hz, 2H), 3.96 (s, 3H), 3.00 (s, 3H), 1.53 (t, J = 7.1 Hz, 3H); ^{13}C NMR (63 MHz, $CDCl_3$): δ = 164.6, 156.9, 142.1, 142.0, 141.1, 139.1, 130.3, 128.4, 128.4, 127.5, 102.9, 60.8, 28.6, 15.0, 13.7; IR (NaCl): ν = 3384, 2920, 1693, 1431, 1209, 1105, 760 cm^{-1}; elemental analysis calcd. (%) for $C_{15}H_{16}ClN_3O_2$: C 58.92, H 5.27, N 13.74; found: C 59.31, H 5.74, N 13.72.

Chloroquine (54): pale yellow solid; mp 90 °C; ^{1}H NMR (250 MHz, MeOD): δ = 8.36 (d, J = 5.7 Hz, 1H), 8.22 (d, J = 9.1 Hz, 1H), 7.79 (d, J = 2.1 Hz, 1H), 7.43 (dd, J = 9.0, 2.2 Hz, 1H), 6.60 (d, J = 6.1 Hz, 1H), 3.91–3.84 (m, 1H), 2.71–2.60 (m, 6H), 1.73–1.66 (m, 4H), 1.36 (d, J = 6.4 Hz, 3H), 1.08 (t, J = 7.2 Hz, 6H); ^{13}C NMR (63 MHz, MeOD): δ = 152.8, 152.6, 150.2, 136.8, 127.9, 126.3, 124.9, 119.2, 100.3, 53.8, 48.2, 35.3, 31.2, 24.1, 20.8, 11.2; IR (NaCl): ν = 3230, 2917, 2848, 1571, 1450, 1077, 800 cm^{-1}; elemental analysis calcd. (%) for $C_{18}H_{26}ClN_3$: C 67.59, H 8.19, N 13.14; found: C 67.24, H 8.01, N 13.10.

Amodiaquine hydrochloride (55): yellow solid; mp 208 °C; ^{1}H NMR (250 MHz, MeOD): δ = 8.58 (d, J = 9.0 Hz, 1H), 8.41 (dd, J = 6.9, 1.0 Hz, 1H), 7.97 (s, 1H), 7.79 (dd, J = 9.1, 1.9 Hz, 1H), 7.56 (d, J = 1.5 Hz, 1H), 7.46 (dd, J = 8.7, 1.6 Hz, 1H), 7.15 (dd, J = 8.7, 0.8 Hz, 1H), 6.84 (dd, J = 6.9, 1.0 Hz, 1H), 4.41 (s, 2H), 3.37–3.25 (m, 4H), 1.42 (t, J = 7.2 Hz, 6H); ^{13}C NMR (63 MHz, MeOD): δ = 158.1, 157.4, 145.6, 142.1, 141.3, 131.6, 130.8, 130.6, 129.3, 126.6, 121.7, 119.8, 118.4, 117.8, 102.1, 52.8, 49.2 (2C), 9.6 (2C) ppm; IR (KBr disk): ν = 1565, 1535, 1255, 869, 847, 815 cm^{-1}; elemental analysis calcd. (%) for $C_{20}H_{23}Cl_2N_3O$: C 61.23, H 5.91, N 10.71; found: C 61.31, H 6.11, N 10.89.

Mepacrine (56): yellow solid; mp 248 °C; ^{1}H NMR (250 MHz, $CDCl_3$): δ = 8.12 (d, J = 2.1 Hz, 1H), 8.04 (d, J =

9.4 Hz, 2H), 7.46 (dd, $J=9.4$, 2.7 Hz, 1H), 7.37 (dd, $J=9.3$, 2.1 Hz, 1H), 7.26 (d, $J=2.6$ Hz, 1H), 4.49 (br d, $J=10.7$ Hz, 1H), 4.11–4.00 (m, 1H), 4.01 (s, 3H), 2.55–2.40 (m, 6H), 1.74–1.62 (m, 4H), 1.30 (d, $J=6.4$ Hz, 3H), 1.00 (t, $J=$ 7.2 Hz, 6H); ^{13}C NMR (63 MHz, $CDCl_3$): $\delta=156.6$, 149.7, 148.6, 147.4, 135.2, 132.0, 128.8, 125.4, 125.1, 124.3, 119.8, 117.8, 99.7, 56.4, 56.0, 53.1, 47.2 (2C), 37.3, 24.3, 22.7, 11.8 (2C); IR (NaCl): $\nu=3260$, 2921, 1628, 1558, 1462, 1434, 1226, 1067, 1028 cm^{-1}; elemental analysis calcd. (%) for $C_{23}H_{30}ClN_3O$: C 69.07, H 7.56, N 10.51; found: C 69.34, H 7.21, N 10.38.

Bis(7)-tacrine (57): yellow solid; mp 66 °C; ^{1}H NMR (250 MHz, MeOD): $\delta=8.07$ (d, $J=8.6$ Hz, 2H), 7.78 (d, $J=$ 8.5 Hz, 2H), 7.54 (t, $J=7.6$ Hz, 2H), 7.34 (t, $J=7.7$ Hz, 2H), 3.48 (t, $J=7.1$ Hz, 4H), 2.98 (br s, 4H), 2.72 (br s, 4H), 1.89 (br s, 8H), 1.59–1.55 (m, 4H), 1.28 (br s, 6H); ^{13}C NMR (63 MHz, MeOD): $\delta=159.6$ (2C), 153.6 (2C), 148.4 (2C), 130.1 (2C), 128.4 (2C), 125.1 (2C), 124.8 (2C), 121.7 (2C), 117.2 (2C), 50.0 (2C), 34.6 (2C), 32.5 (2C), 30.4, 28.2 (2C), 26.6 (2C), 24.5 (2C), 24.2 (2C); IR (NaCl): $\nu=1614$, 1580, 1561, 1498, 1420, 1358, 1296, 1272, 678 cm^{-1}; elemental analysis calcd. (%) for $C_{33}H_{40}N_4$: C 80.45, H 8.18, N 11.37; found: C 80.05, H 8.07, N 11.50.

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References

[1] a) A. F. Pozharskii, A. T. Soldartenkov, A. R. Katrizky, *Heterocycles in Life and Society*, 2nd edn., John Wiley & Sons, Weinheim, **2011**; b) W. R. Pitt, D. M. Parry, B. G. Perry, C. R. Groom, *J. Med. Chem.* **2009**, *52*, 2952–2963.

[2] a) S. Bongarzone, M. L. Bolognesi, *Expert Opin. Drug Discovery* **2011**, *6*, 251–268; b) J. Polanski, A. Kurczyk, A. Bak, R. Musiol, *Curr. Med. Chem.* **2012**, *19*, 1921–1945.

[3] a) S. Ray, P. Sadhukhan, N. Mandal, S. Mahato, H. Majumder, *Biochem. Biophys. Res. Commun.* **1997**, *230*, 171–175; b) G. Chakrabarti, A. Basu, P. Manna, S. Mahato, N. Mandal, S. Bandyopadhyay, *J. Antimicrob. Chemother.* **1999**, *43*, 359–366.

[4] G. Marzaro, A. Guiotto, A. Chilin, *Expert Opin. Ther. Patents* **2012**, *22*, 223–252.

[5] a) M. Demeunynck, F. Charmantray, A. Martelli, *Curr. Pharm. Des.* **2001**, *7*, 1703–1724; b) W. A. Denny, *Curr. Med. Chem.* **2002**, *9*, 1655–1665.

[6] J. W. Tracy, L. T. Webster Jr, in: *Goodman and Gilman's The Pharmacological Basis of Therapeutics*, (Eds.: J. G. Hardman, L. E. Limbird), McGraw Hill, New York, **2001**, p 1111.

[7] a) M. O. Anderson, J. Sherrill, P. B. Madrid, A. P. Liou, J. L. Weisman, J. L. De Risib, R. Kiplin Guy, *Bioorg. Med. Chem.* **2006**, *14*, 334–343; b) T. H. Nguyen, C. Y. Lee, K. Teruya, W. Y. Ong, K. Doh-ura, M. L. Go, *Bioorg. Med. Chem.* **2008**, *16*, 6737–6746; c) M. Vogtherr, S. Grimme, B. Elshorst, D. M. Jacobs, K. Fiebig, C. Griesinger, R. Zahn, *J. Med. Chem.* **2003**, *46*, 3563–3564; d) B. C. May, A. T. Fafarman, S. B. Hong, M. Rogers, L. W. Deady, S. B. Prusiner, F. E. Cohen, *Proc. Natl. Acad. Sci. USA* **2003**, *100*, 3416–3421; e) A. Cavalli, F. Lizzi, S. Bongarzone, R. Brun, R. L. Krauth-Siegel, M. L. Bolognesi, *Bioorg. Med. Chem. Lett.* **2009**, *19*, 3031–3035.

[8] For a review, see: M. González, H. Cerecetto, *Exp. Opin. Ther. Patents* **2012**, *22*, 1289–1302.

[9] a) S. A. Laufer, D. M. Domeyer, T. R. F. Scior, W. Albrecht, D. R. J. Hauser, *J. Med. Chem.* **2005**, *48*, 710–722; b) M. Zatloukal, M. Gemrotová, K. Doležal, L. Havlíček, L. Spíchal, M. Strnad, *Bioorg. Med. Chem.* **2008**, *16*, 9268–9275.

[10] M. E. Welsch, S. A. Snyder, B. R. Stockwell, *Curr. Opin. Chem. Biol.* **2010**, *14*, 347–361.

[11] a) Z. M. Nofal, H. H. Fahmy, H. S. Mohamed, *Arch. Pharmacal Res.* **2002**, *25*, 250–257; b) U. S. Sørensen, D. Strøbæk, P. Christophersen, C. Hougaard, M. L. Jensen, E. Ø. Nielsen, D. Peters, L. Teuber, *J. Med. Chem.* **2008**, *51*, 7625–7634.

[12] a) J. Payack, E. Vázquez, L. Matty, M. Kress, J. McNamara, *J. Org. Chem.* **2005**, *70*, 175–178; b) A. Nishida, N. Miyashita, M. Fuwa, M. Nakagawa, *Heterocycles* **2003**, *59*, 473–476; c) M. J. Iglesias, A. Prieto, M. C. Nicasio, *Adv. Synth. Catal.* **2010**, *352*, 1949–1954; d) L. Chen, G. A. Yu, F. Li, X. Zhu, B. Zhang, R. Guo, X. Li, Q. Yang, S. Jin, C. Liu, S. H. Liu, *J. Organomet. Chem.* **2010**, *695*, 1768–1775; e) I. V. Seregin, V. Gevorgyan, *Chem. Soc. Rev.* **2007**, *36*, 1173–1193; f) S. Wagaw, S. L. Buchwald, *J. Org. Chem.* **1996**, *61*, 7240–7241.

[13] a) M. Yamaguchi, K. Kamei, T. Koga, M. Akima, A. Maruyama, T. Kuroki, N. Ohi, *J. Med. Chem.* **1993**, *36*, 4052–4060; b) A. Luth, W. Lowe, *Eur. J. Med. Chem.* **2008**, *43*, 1478–1488.

[14] a) J. Kuethe, A. Wong, I. Davies, *Org. Lett.* **2003**, *5*, 3975–3978; b) S. Zhu, S. Ji, K. Zhao, Y. Liu, *Tetrahedron Lett.* **2008**, *49*, 2578–2582; c) M. Lian, Q. Li, Y. Zhu, G. Yin, A. Wu, *Tetrahedron* **2012**, *68*, 9598–9605; d) S. Kamila, H. Ankati, E. R. Biehl, *Arkivoc*, **2011**, *9*, 94–104.

[15] K. Ohkura, K. Seki, M. Terashima, Y. Kanaoka, *Heterocycles* **1990**, *30*, 957–962.

[16] M. Chahma, C. Combellas, A. Thiébault, *Synthesis* **1994**, 366–368.

[17] a) M. Brasse, J. A. Ellman, R. G. Bergman, *Chem. Commun.* **2011**, *47*, 5019–5021; b) Y. A. Azev, S. V. Shorshnev, B. V. Golomolzin, *Tetrahedron Lett.* **2009**, *50*, 2899–2903; c) T. Higashino, Y. Kawade, E. Hayashi, *Heterocycles* **1977**, *8*, 159–164.

[18] T. N. Birkinshaw, S. J. Teague, C. Beech, R. V. Bonnert, S. Hill, A. Patel, S. Reakes, H. Sanganee, I. G. Dougall, T. T. Phillips, S. Salter, J. Schmidt, E. C. Arrowsmith, J. J. Carrillo, F. M. Bell, S. W. Pained, R. Weaver, *Bioorg. Med. Chem. Lett.* **2006**, *16*, 4287–4290.

[19] a) M. Pal, V. R. Batchu, K. Parasuraman, K. R. Yeleswarapu, *J. Org. Chem.* **2003**, *68*, 6806–6809; b) M. Pal, V. R. Batchu, I. Dager, N. K. Swamy, S. Padakanti, *J.*

Org. Chem. **2005**, *70*, 2376–2379; c) S. Kumar, D. P. Sahu, *J. Heterocycl. Chem.* **2009**, *46*, 748–755.
[20] V. Sridharan, C. Avendaño, J. C. Menéndez, *Synlett* **2007**, *6*, 881–884.
[21] For reviews, see: a) B. Govindh, B. S. Diwakar, Y. L. N. Murthy, *Org. Commun.* **2012**, *5*, 105–119; b) A.-Z. A. Elassar, A. A. El-Khair, *Tetrahedron* **2003**, *59*, 8463–8480.
[22] For leading references of β-enaminone-initiated multicomponent reactions from our group, see: a) G. Tenti, E. Parada, R. León, J. Egea, S. Martínez-Revelles, A. M. Briones, V. Sridharan, M. G. López, M. T. Ramos, J. C. Menéndez, *J. Med. Chem.* **2014**, *57*, 4313–4323; b) P. A. Suryavanshi, V. Sridharan, J. C. Menéndez, *Chem. Eur. J.* **2013**, *19*, 13207–13215.
[23] For representative examples, see: a) M. A. Alonso, P. López-Alvarado, C. Avendaño, J. C. Menéndez, *Tetrahedron* **2003**, *59*, 2821–2830; b) S. Manzanaro, M. J. Vicent, M. J. Martín, N. Salvador-Tormo, J. M. Pérez, M. M. Blanco, C. Avendaño, J. C. Menéndez, J. A. de La Fuente, *Bioorg. Med. Chem.* **2004**, *12*, 6505–6515.
[24] M. Staderini, N. Cabezas, M. L. Bolognesi, J. C. Menéndez, *Tetrahedron* **2013**, *69*, 1024–1030.
[25] a) M. V. N. de Souza, K. C. Pais, C. R. Kaiser, M. A. Peralta, M. de L. Ferreira, M. C. S. Lourenço, *Bioorg. Med. Chem.* **2009**, *17*, 1474–1480; b) A. S. Ressurreição, D. Gonçalves, A. R. Sitoe, I. S. Albuquerque, J. Gut, A. Góis, L. M. Gonçalves, M. R. Bronze, T. Hanscheid, G. A. Biagini, P. J. Rosenthal, M. Prudêncio, P. O'Neill, M. M. Mota, F. Lopes, R. Moreira, *J. Med. Chem.* **2013**, *56*, 7679–7690.
[26] Z. Y. Xing, Y. Fu, F. Ye, *J. Heterocycl. Chem.* **2012**, *49*, 1210–1213.
[27] Z. K. Wan, S. Wacharasindhu, C. G. Levins, M. Lin, K. Tabei, T. S. Mansour, *J. Org. Chem.* **2007**, *72*, 10194–10210.
[28] a) R. Saari, J. C. Törmä, T. Nevalainen, *Bioorg. Med. Chem.* **2011**, *19*, 939–950; b) R. A. Smits, H. D. Lim, A. Hanzer, O. P. Zuiderveld, E. Guaita, M. Adami, G. Coruzzi, R. Leurs, I. J. de Esch, *J. Med. Chem.* **2008**, *51*, 2457–2467; c) C. Iijima, T. Kyo, *Chem. Pharm. Bull.* **1989**, *37*, 618–620.
[29] a) L. K. Huang, Y. C. Cherng, Y. R. Cheng, J. P. Jang, Y. L. Chao, Y. J. Cherng, *Tetrahedron* **2007**, *63*, 5323–5327; b) G. Qu, S. Han, Z. Zhang, M. Geng, F. Xue, *J. Braz. Chem. Soc.* **2006**, *17*, 915–922; c) E. Adamska, J. Barciszewski, W. T. Markiewicz, *Nucleosides Nucleotides Nucleic Acids* **2012**, *31*, 861–871.
[30] a) R. Yella, B. K. Patel, *J. Comb. Chem.* **2010**, *12*, 754–763; b) S. K. Verma, B. N. Acharya, M. P. Kaushik, *Org. Biomol. Chem.* **2011**, *9*, 1324–1327.
[31] K. Kaur, M. Jain, R. P. Reddy, R. Jain, *Eur. J. Med. Chem.* **2010**, *45*, 3245–3264.
[32] V. Tumiatti, A. Minarini, M. L. Bolognesi, A. Milelli, M. Rosini, C. Melchiorre, *Curr. Med. Chem.* **2010**, *17*, 1825–1838.