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Regioselective *N*-alkylation with alcohols for the preparation of 2-(*N*-alkylamino)quinazolines and 2-(*N*-alkylamino)pyrimidines†

Feng Li,* Lin Chen, Qikai Kang, Jianguang Cai and Guangjun Zhu

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In the presence of the $[Cp^*IrCl_2]_2$/NaOH system, the direct *N*-alkylation of 2-aminoquinazolines and 2-aminopyrimidines with alcohols afforded the *N*-exosubstituted 2-(*N*-alkylamino)quinazolines and 2-(*N*-alkylamino)pyrimidines with 71–96% yields and complete regioselectivities. The protocol is highly attractive because of easily available starting materials, high atom efficiency and environmental friendliness.

Introduction

2-Aminoquinazoline and 2-aminopyrimidine are ubiquitous structural motifs of many natural products and pharmaceutically active compounds. In particular, 2-(*N*-alkylamino)quinazolines and 2-(*N*-alkylamino)pyrimidines exhibit a wide range of biological properties.[1] Selective examples include potent p38 inhibitors (**A**),[1a] lymphocyte-specific kinase (Lck) inhibitors (**B**),[1b] dual orexin receptor antagonists (**C**),[1c] cyclin-dependent kinase inhibitors (**D**),[1d] *N*-methyl-D-aspartate receptor antagonists (**E**)[1e] and histamine H4 receptor antagonists (**F**)[1f] (Fig. 1). Traditionally, 2-(*N*-alkylamino)quinazolines and 2-(*N*-alkylamino)-pyrimidines were prepared by S_NAr reactions of 2-haloquinazolines and 2-halopyrimidines with alkylamines.[1] These methods suffer from the multistep synthesis of starting materials, the use of excess amount of hypertoxic phosphorus oxychloride in the conversion from quinazolinones and pyrimidinones to 2-haloquinazolines and 2-halopyrimidines, and the formation of stoichiometric amount of halogen acids as side products (Scheme 1). In the past few years, solid-phase synthesis[2a] and intramolecular cyclization[2b] have been developed for the synthesis of 2-(*N*-alkylamino)quinazolines. However, these two procedures are only available for the preparation of 2-(*N*-alkylamino)-4-aminoquinazolines[2a] and 2-(*N*-alkylamino)-4-phenylquinazolines,[2b] and thus the synthetic potential is highly restricted.

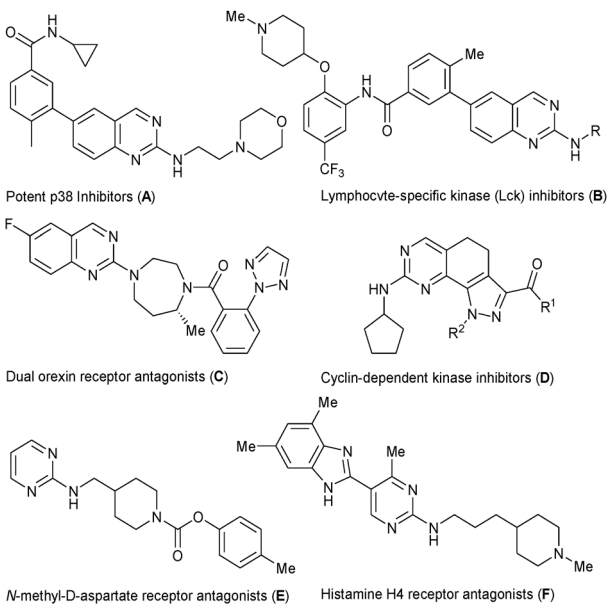
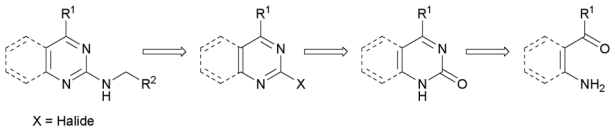


Fig. 1 Biologically active 2-(*N*-alkylamino)quinazolines and 2-(*N*-alkylamino)-pyrimidines.

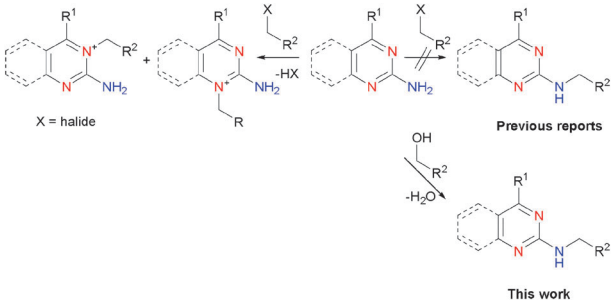
The direct *N*-alkylation of 2-aminoquinazolines and 2-aminopyrimidines provides one of the most simple and ideal routes to 2-(*N*-alkylamino)quinazolines and 2-(*N*-alkylamino)pyrimidines. However, such reactions using alkyl halides as alkylating agents afforded the *N*-endosubstituted products due to the endocyclic nitrogens being more basic than the exocyclic ones (Scheme 2, top line).[3] In recent years, much attention has been paid to the *N*-alkylation of amines with alcohols as alkylating agents based on "hydrogen autotransfer (or hydrogen-borrowing) process",[4]

School of Chemical Engineering, Nanjing University of Science and Technology, Nanjing 210094, P. R. China. E-mail: fengli@njust.edu.cn; Fax: +86-25-84431939; Tel: +86-25-84317316

† Electronic supplementary information (ESI) available: Copies of the ^1H NMR and ^{13}C NMR spectra for all *N*-alkylated products. See DOI: 10.1039/c2nj41021d



Scheme 1 Traditional methods for the preparation of 2-(*N*-alkylamino)-quinazolines and 2-(*N*-alkylamino)pyrimidines.



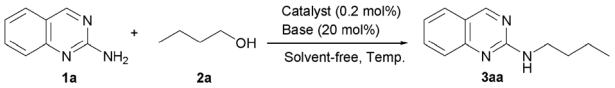
Scheme 2 Regioselective *N*-alkylation of 2-aminoquinazolines and 2-aminopyrimidines with alkyl halides or alcohols.

using iridium,[5] ruthenium[6] or other transition metal catalysts.[7] In this process, alcohols are first dehydrogenated to form aldehydes, followed by the condensation of the resulting aldehydes with amines to afford imine intermediates, which are hydrogenated to give the final *N*-alkylated products. The methodology is attractive because of high atom efficiency and the formation of water as the only side product. Very recently, we reported transition metal-catalyzed direct *N*-alkylation of 2-aminoazoles with alcohols to the corresponding 2-(*N*-alkylamino)azoles, exhibiting the potential of alcohols rather than alkyl halides as electrophilics in regioselective reactions.[8] We also demonstrated iridium-catalyzed regioselective *N*3-alkylation of *N*-monosubstituted ureas with alcohols for the synthesis of *N,N′*-alkylarylureas and *N,N′*-dialkylureas.[9] As part of continuing interest in this field, we herein wish to describe our efforts towards direct *N*-alkylation with alcohols as alkylating agents for the preparation of 2-(*N*-alkylamino)quinazolines and 2-(*N*-alkylamino)pyrimidines. (Scheme 2, bottom line).

Results and discussion

Initially, the *N*-alkylation of 2-aminoquinazoline **1a** with 1-butanol **2a** was chosen as a model. The reaction was carried out in the presence of commercially available $[Cp^*IrCl_2]_2$ (Cp^* = pentamethylcyclopentadienyl) (0.2 mol%) at 150 °C for 12 h and no product was detected (Table 1, entry 1). In the presence of a base such as K_2CO_3 and Cs_2CO_3, the reaction afforded the desired product **3aa** with 53% and 72% yields, respectively (entries 2 and 3). Further, the product **3aa** was obtained with almost quantitative yield in the presence of the strong base such as NaOH, KOH or NaO*t*Bu (entries 4–6). Among them, NaOH was selected as the base for further research. Using $[Ir(cod)Cl]_2$ (cod = 1,5-cyclooctadienyl) as an alternative catalyst, the product was obtained with 51% yield (entry 7). It was also found that no reaction took place in the presence of NaOH alone (entry 8). Attempts to decrease the reaction temperature resulted in relatively low yields (entries 9 and 10).

Table 1 *N*-Alkylation of 2-aminoquinazoline **1a** with 1-butanol **2a** under various conditions[a]



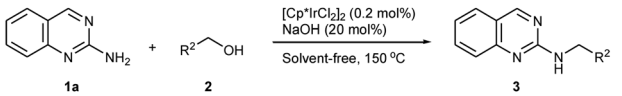
Entry	Catalyst	Base	Temp./°C	Yield[b] (%)
1	$[Cp^*IrCl_2]_2$	—	150	0
2	$[Cp^*IrCl_2]_2$	K_2CO_3	150	53
3	$[Cp^*IrCl_2]_2$	Cs_2CO_3	150	72
4	$[Cp^*IrCl_2]_2$	NaOH	150	96
5	$[Cp^*IrCl_2]_2$	KOH	150	92
6	$[Cp^*IrCl_2]_2$	NaO*t*Bu	150	90
7	$[Ir(cod)Cl]_2$	NaOH	150	51
8	—	NaOH	150	0
9	$[Cp^*IrCl_2]_2$	NaOH	130	78
10	$[Cp^*IrCl_2]_2$	NaOH	110	70

[a] Reaction conditions: 1 mmol **1a**, 5 mmol **2a**, 0.2 mol% catalyst, 0.2 mmol base, 150 °C, 12 h. [b] Isolated yield.

Having established the optimal reaction condition (Table 1, entry 4), the *N*-alkylation of **1a** with a variety of alcohols **2** was examined and the results are summarized in Table 2. Similar to the case of **2a**, the long-chain aliphatic primary alcohols, such as 1-hexanol **2b** and 1-octanol **2c**, were utilized to afford the corresponding products **3ab** and **3ac** with 95% and 92% yields, respectively (Table 2, entries 1 and 2). The short-chain aliphatic primary alcohols such as ethanol **2d** were also proven to be a suitable alkylating agent, although the desired product **3ad** was obtained with 71% yield (entry 3). Further, reactions with the branched aliphatic primary alcohols **2e–g** gave the corresponding products **3ae–3ag** with 91–96% yields (entries 4–6). The cyclic primary alcohol **2h** and the cyclic secondary alcohol with high steric hindrance **2i**, were successfully converted to afford the desired products **3ah** and **3ai** with 91% and 85% yields, respectively (entries 7 and 8). High activities were also found in the *N*-alkylation of 2-phenylethanol **2j** and 3-phenylpropanol **2k**, and the corresponding products **3aj** and **3ak** were obtained with 83% and 93% yields, respectively (entries 9 and 10). When benzyl-type alcohols **2l–o** were used as substrates, reactions afforded the desired products **3al–3ao** with 80–90% yields (entries 11–14).

To further expand the scope of the reaction, the *N*-alkylation of a series of 2-aminoquinzolines and 2-aminopyrimidines **1** with **2a** was then investigated. As outlined in Table 3, reactions of 2-aminoquinazolines bearing an electron-donating group **1b** and an electron-withdrawing group **1c** afforded the corresponding products **3ba** and **3ca** with 80% and 81% yields, respectively (Table 3, entries 1 and 2). Similarly, the *N*-alkylation of 2-aminoquinazolines bearing a halide atom **1d** and **1e** gave the desired products **3da** and **3ea** with 86% and 89% yields, respectively (entries 3 and 4). The 2-aminoquinazoline bearing a substituent at the 4 position **1f** was alkylated to the corresponding product **3fa** with 83% yield (entry 5). In the case of 2-aminopyrimidine **1g**, the desired product **3ga** was obtained with 95% yield (entry 6).

Table 2 *N*-Alkylation of 2-aminoquinazoline **1a** with various alcohols **2**[a]



1a 2 3

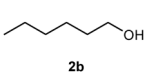
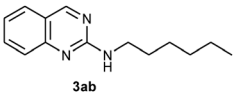
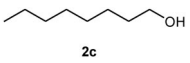
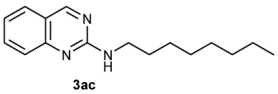
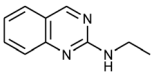
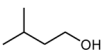
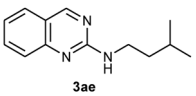
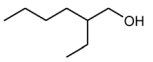
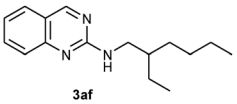
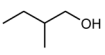
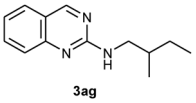
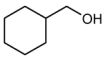
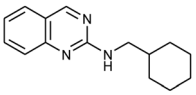
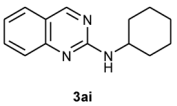
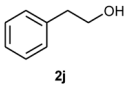
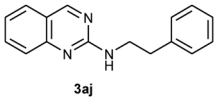
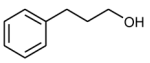
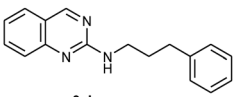
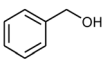
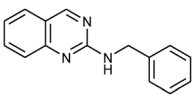
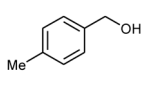
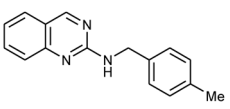
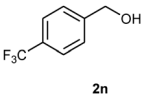
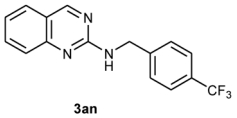
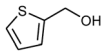
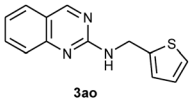
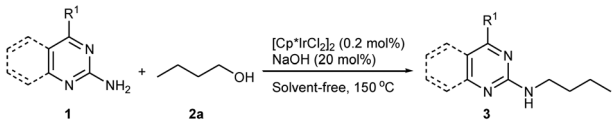
Entry	Alcohol	Product	Yield[b] (%)
1	 2b	 3ab	95
2	 2c	 3ac	92
3	 2d	 3ad	71[c]
4	 2e	 3ae	96
5	 2f	 3af	91
6	 2g	 3ag	94
7	 2h	 3ah	91
8	 2i	 3ai	85[d]
9	 2j	 3aj	83
10	 2k	 3ak	93
11	 2l	 3al	84
12	 2m	 3am	83

Table 2 (*continued*)

Entry	Alcohol	Product	Yield[b] (%)
13	 2n	 3an	80
14	 2o	 3ao	90

[a] Reaction conditions: 1 mmol **1a**, 5 mmol **2**, 0.2 mol% $[Cp^*IrCl_2]_2$, 0.2 mmol NaOH, 150 °C, 12 h. [b] Isolated yield. [c] 1 mmol NaOH. [d] 0.4 mmol NaOH.

Table 3 *N*-Alkylation of a series of 2-aminoquinazolines and 2-aminopyrimidines **1** with 1-butanol **2a**[a]



1 2a 3

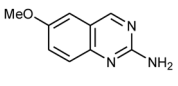
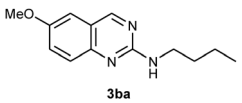
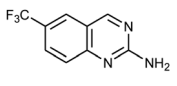
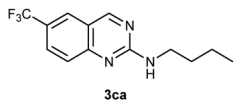
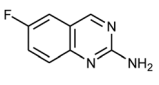
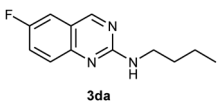
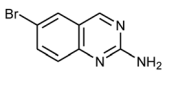
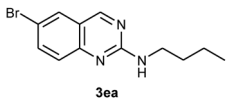
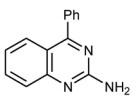
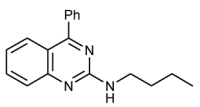
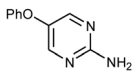
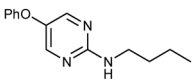
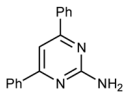
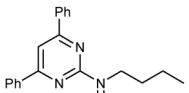
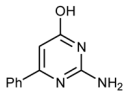
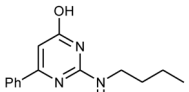
Entry	Amine	Product	Yield[b] (%)
1	 1b	 3ba	80
2	 1c	 3ca	81
3	 1d	 3da	86[c]
4	 1e	 3ea	89
5	 1f	 3fa	83[c]
6	1g	3ga	95
7	1h	3ha	86

Table 3 (*continued*)

Entry	Amine	Product	Yield[b] (%)
8	 1i	 3ia	91
9	 1j	 3ja	71[c]
10	 1k	 3ka	85[d]

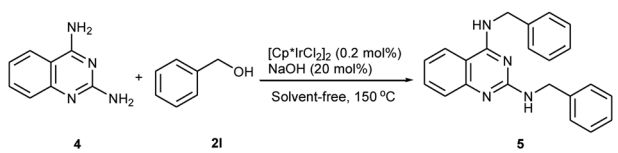
[a] Reaction conditions: 1 mmol amine, 5 mmol alcohol, 0.2 mol% $[Cp^*IrCl_2]_2$, 0.2 mmol NaOH, 150 °C, 12 h. [b] Isolated yield. [c] 1 mmol NaOH. [d] 0.4 mmol NaOH.

Transformations of 2-aminopyrimidines bearing one and two substituents **1h–1j** afforded the corresponding products **3ha–3ja** with 71–91% yields (entries 7–9). The reaction was also applied to 2-amino-6-phenylpyrimidin-4-ol **1k** (the tautomerism of 2-amino-6-phenylpyrimidin-4(1H)-one) and the desired product **3ka** was produced with 85% yield (entry 10).

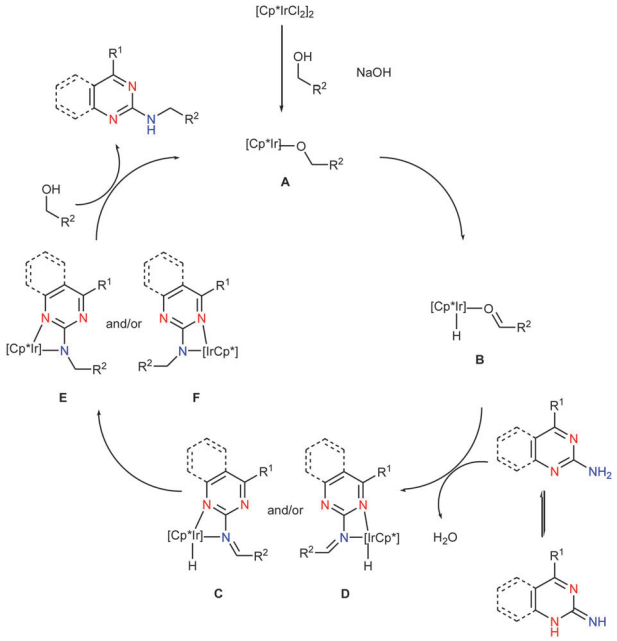
The *N*-alkylation of 2,4-diaminoquinazoline with alcohol was also investigated. As shown in Scheme 3, the reaction of **4** (1 mmol) with **2l** (5 mmol) was carried out for 12 h, affording the corresponding *N*2,*N*4-dialkylated products **5** with 81% yield.

It should be noted that apart from the desired *N*-exosubstituted products, no isomer (the *N*-endosubstituted products) and over-alkylated products were observed in all cases. In addition, more than 20 mol% NaOH was required in a few cases to obtain the products with high yields.

Based on the experimental results, a possible mechanism is proposed to account for the regioselective reaction (Scheme 4). The alcohols are first dehydrogenated to form the aldehydes coordinated with iridium hydride species **B**.[10] Obviously, the exocyclic nitrogens are favored over the endocyclic ones of 2-aminoquinazolines or 2-aminopyrimidines in the condensation with the resulting **B**, giving the corresponding imines coordinated with iridium hydride species **C** and/or **D**. The addition of iridium hydride into the C=N bond of imines afforded the amido–iridium species **E** and/or **F**. Finally, the *N*-exosubstituted products were obtained and the catalytically active alkoxo iridium species **A** were generated *via* amido–alkoxo exchange reaction.[11,12]



Scheme 3 *N*-Alkylation of 2,4-diaminoquinazoline **4** with benzyl alcohol **2l**.



Scheme 4 The proposed reaction mechanism.

Conclusion

We have developed a simple, efficient and general method for the preparation of 2-(*N*-alkylamino)quinazolines and 2-(*N*-alkylamino)pyrimidines *via* direct *N*-alkylation of the corresponding amines with alcohols catalyzed by the $[Cp^*IrCl_2]_2$/NaOH system. From a synthetic point of view, the protocol is highly attractive because of easily available starting materials, high atom efficiency, broad substrate scope and environmental friendliness. Further studies to explore new potential of alcohols as electrophiles are under way.

Experimental section

General experimental details

High-resolution mass spectra (HRMS) were obtained on a HPLC-Q-Tof MS(Micro) spectrometer and are reported as *m*/*z* (relative intensity). Accurate masses are reported for the molecular ion $[M + H]^+$. Melting points were measured on a X-6 micro-melting apparatus (Beijing Tech Instrument Co., Ltd). Proton nuclear magnetic resonance (^{1}H NMR) spectra were recorded at 500 MHz using a Bruker Avance 500 spectrometer. Chemical shifts are reported in delta (δ) units, parts per million (ppm) downfield from trimethylsilane or ppm relative to the center of the singlet at 7.26 ppm for $CDCl_3$. Coupling constants *J* values are reported in Hertz (Hz), and the splitting patterns were designated as follows: s, singlet; d, doublet; t, triplet; m, multiplet; b, broad. Carbon-13 nuclear magnetic resonance (^{13}C NMR) spectra were recorded at 125 MHz using a Bruker Avance 500 spectrometer. Chemical shifts are reported in delta

(δ) units, ppm relative to the center of the triplet at 77.0 ppm for $CDCl_3$. ^{13}C NMR spectra were routinely run with broadband decoupling. All reactions were run under an atmosphere of nitrogen, unless otherwise indicated. Analytical thin-layer chromatography (TLC) was carried out using 0.2 mm commercial silica gel plates.

General procedure for *N*-alkylation of 2-aminoquinazolines and 2-aminopyrimidines with alcohols catalyzed by the $[Cp^*IrCl_2]_2$/NaOH system. To an oven-dried, nitrogen purged 25 ml Schlenk tube were added 2-aminoquinazolines or 2-aminopyrimidines (1 mmol), alcohol (5 mmol), NaOH (0.2 mmol, 20 mol%) and $[Cp^*IrCl_2]_2$ (0.002 mmol, 0.2 mol%). The mixture was heated at 150 °C for 12 h and was then allowed to cool to ambient temperature. The reaction mixture was concentrated *in vacuo* and purified by flash column chromatography with hexane/ethyl acetate to afford the corresponding product.

***N*-Butylquinazolin-2-amine (3aa).** mp 49–50 °C; ^1H NMR (500 MHz, $CDCl_3$) δ 8.95 (s, 1H, ArH), 7.68–7.64 (m, 2H, ArH), 7.58 (d, J = 8.5 Hz, 1H, ArH), 7.21 (t, J = 7.4 Hz, 1H, ArH), 5.21 (br s, 1H, NH), 3.55 (quart, J = 6.6 Hz, 2H, CH_2N), 1.66 (quint, J = 7.3 Hz, 2H, CH_2), 1.47 (sext, J = 7.4 Hz, 2H, CH_2), 0.98 (t, J = 5.9 Hz, 3H, CH_3); ^{13}C NMR (125 MHz, $CDCl_3$) δ 161.9, 159.8, 152.3, 134.1, 127.6, 125.6, 122.4, 120.2, 41.4, 31.8, 20.2, 13.9; HRMS-EI (70 eV) m/z calcd for $C_{12}H_{16}N_3$ $[M + H]^+$ 202.1344, found 202.1341.

***N*-Hexylquinazolin-2-amine (3ab).** mp 73–74 °C; ^1H NMR (500 MHz, $CDCl_3$) δ 8.95 (s, 1H, ArH), 7.68–7.64 (m, 2H, ArH), 7.58 (d, J = 8.6 Hz, 1H, ArH), 7.21 (t, J = 7.5 Hz, 1H, ArH), 5.24 (br s, 1H, NH), 3.54 (quart, J = 6.6 Hz, 2H, CH_2N), 1.67 (quint, J = 7.3 Hz, 2H, CH_2), 1.43 (quint, J = 7.3 Hz, 2H, CH_2), 1.35–1.32 (m, 4H, 2xCH_2), 0.90 (t, J = 7.0 Hz, 3H, CH_3); ^{13}C NMR (125 MHz, $CDCl_3$) δ 161.9, 159.7, 152.3, 134.2, 127.5, 125.5, 122.3, 120.1, 41.6, 31.6, 29.6, 26.7, 22.6, 14.0; HRMS-EI (70 eV) m/z calcd for $C_{14}H_{20}N_3$ $[M + H]^+$ 230.1657, found 230.1654.

***N*-Octylquinazolin-2-amine (3ac).** mp 70–72 °C; ^1H NMR (500 MHz, $CDCl_3$) δ 8.95 (s, 1H, ArH), 7.68–7.64 (m, 2H, ArH), 7.58 (d, J = 8.5 Hz, 1H, ArH), 7.21 (t, J = 7.5Hz, 1H, ArH), 5.24 (br s, 1H, NH), 3.54 (quart, J = 6.6 Hz, 2H, CH_2N), 1.67 (quint, J = 7.3 Hz, 2H, CH_2), 1.43 (quint, J = 7.3 Hz, 2H, CH_2), 1.38–1.28 (m, 8H, 4xCH_2), 0.88 (t, J = 7.0 Hz, 3H, CH_3); ^{13}C NMR (125 MHz, $CDCl_3$) δ 161.9, 159.8, 152.3, 134.1, 127.5, 125.5, 122.3, 120.2, 41.6, 31.8, 29.6, 29.3, 29.2, 27.0, 22.6, 14.1; HRMS-EI (70 eV) m/z calcd for $C_{16}H_{24}N_3$ $[M + H]^+$ 258.1970, found 258.1975.

***N*-Ethylquinazolin-2-amine (3ad).**[13] mp 88–89 °C (lit.[13] mp 96–97 °C); ^1H NMR (500 MHz, $CDCl_3$) δ 8.96 (s, 1H, ArH), 7.68–7.64 (m, 2H, ArH), 7.59 (d, J = 8.4 Hz, 1H, ArH), 7.21 (t, J = 7.4 Hz, 1H, ArH), 5.26 (br s, 1H, NH), 3.58 (quint, J = 6.9 Hz, 2H, CH_2), 1.30 (t, J = 7.3 Hz, 3H, CH_3); ^{13}C NMR (125 MHz, $CDCl_3$) δ 161.9, 159.7, 152.3, 134.2, 127.5, 125.6, 122.4, 120.2, 36.5, 14.8.

***N*-Isopentylquinazolin-2-amine (3ae).** mp 68–69 °C; ^1H NMR (500 MHz, $CDCl_3$) δ 8.95 (s, 1H, ArH), 7.68–7.64 (m, 2H, ArH), 7.58 (d, J = 8.4 Hz, 1H, ArH), 7.21 (t, J = 7.4 Hz, 1H, ArH), 5.20 (br s, 1H, NH), 3.56 (quart, J = 6.8 Hz, 2H, CH_2N), 1.79–1.71 (m, 1H, CH), 1.56 (quart, J = 7.3 Hz, 2H, CH_2), 0.97 (d, J = 6.6 Hz, 6H, 2xCH_3); ^{13}C NMR (125 MHz, $CDCl_3$) δ 161.9, 159.8, 152.3, 134.1, 127.5, 125.5, 122.3, 120.1, 39.9, 38.6, 25.8, 22.6; HRMS-EI (70 eV) m/z calcd for $C_{13}H_{18}N_3$ $[M + H]^+$ 216.1501, found 216.1503.

***N*-(2-Ethylhexyl)quinazolin-2-amine (3af).** mp 47–48 °C; ^1H NMR (500 MHz, $CDCl_3$) δ 8.95 (s, 1H, ArH), 7.67–7.63 (m, 2H, ArH), 7.57 (d, J = 8.4 Hz, 1H, ArH), 7.20 (t, J = 7.4 Hz, 1H, ArH), 5.26 (br s, 1H, NH), 3.54–3.45 (m, 2H, CH_2N), 1.63–1.57 (m, 1H, CH), 1.48–1.30 (m, 8H, 4xCH_2), 0.94 (t, J = 7.4 Hz, 3H, CH_3), 0.90 (t, J = 7.1 Hz, 3H, CH_3); ^{13}C NMR (125 MHz, $CDCl_3$) δ 161.9, 160.0, 152.2, 134.1, 127.5, 125.5, 122.3, 120.1, 44.3, 39.5, 31.2, 29.0, 24.4, 23.1, 14.1, 11.0; HRMS-EI (70 eV) m/z calcd for $C_{16}H_{24}N_3$ $[M + H]^+$ 258.1970, found 258.1971.

***N*-(2-Methylbutyl)quinazolin-2-amine (3ag).** mp 94–95 °C; ^1H NMR (500 MHz, $CDCl_3$) δ 8.95 (s, 1H, ArH), 7.67–7.63 (m, 2H, ArH), 7.58 (d, J = 8.2 Hz, 1H, ArH), 7.20 (t, J = 7.3 Hz, 1H, ArH), 5.31 (br s, 1H, NH), 3.50 (quint, J = 6.3 Hz, 1H, CHN), 3.37 (quint, J = 6.2 Hz, 1H, CHN), 1.79–1.70 (m, 1H, CH), 1.53 (sept, J = 6.9 Hz, 1H, CH), 1.26 (sept, J = 7.3 Hz, 1H, CH), 1.00 (d, J = 6.8 Hz, 3H, CH_3), 0.95 (t, J = 7.4 Hz, 3H, CH_3); ^{13}C NMR (125 MHz, $CDCl_3$) δ 161.9, 159.9, 152.2, 134.1, 127.5, 125.5, 122.4, 120.1, 47.3, 34.9, 27.4, 17.5, 11.6; HRMS-EI (70 eV) m/z calcd for $C_{13}H_{18}N_3$ $[M + H]^+$ 216.1501, found 216.1498.

***N*-(Cyclohexylmethyl)quinazolin-2-amine (3ah).** mp 138–139 °C; ^1H NMR (500 MHz, $CDCl_3$) δ 8.94 (s, 1H, CH, ArH), 7.67–7.63 (m, 2H, ArH), 7.57 (d, J = 8.4 Hz, 1H, ArH), 7.20 (t, J = 7.4Hz, 1H, ArH), 5.33 (br s, 1H, NH), 3.41 (t, J = 6.3 Hz, 2H, CH_2N), 1.84 (d, J = 6.6 Hz, 2H, CH_2), 1.76–1.73 (m, 2H, CH_2), 1.69–1.60 (m, 2H, CH_2), 1.30–1.15 (m, 3H, CH_2 and CH), 1.04 (m, 2H, CH_2); ^{13}C NMR (125 MHz, $CDCl_3$) δ 161.8, 160.0, 152.3, 134.1, 127.5, 125.5, 122.2, 120.2, 47.9, 38.0, 31.0, 26.5, 26.0; HRMS-EI (70 eV) m/z calcd for $C_{15}H_{20}N_3$ $[M + H]^+$ 242.1657, found 242.1660.

***N*-Cyclohexylquinazolin-2-amine (3ai) (ref. 14).** mp 111–112 °C; ^1H NMR (500 MHz, $CDCl_3$) δ 8.94 (s, 1H, ArH), 7.66–7.62 (m, 2H, ArH), 7.56 (d, J = 8.6 Hz, 1H, ArH), 7.19 (t, J = 7.4 Hz, 1H, ArH), 5.20 (br s, 1H, NH), 4.04–3.97 (m, 1H, CH), 2.12–2.09 (m, 2H, CH_2), 1.79–1.75 (m, 2H, CH_2), 1.68–1.64 (m, 1H, CH), 1.51–1.42 (m, 2H, CH_2), 1.31–1.24 (m, 3H, CH_2 and CH); ^{13}C NMR (125 MHz, $CDCl_3$) δ 161.9, 159.0, 152.4, 134.0, 127.6, 125.5, 122.3, 120.1, 49.7, 33.3, 25.8, 24.9.

***N*-Phenethylquinazolin-2-amine (3aj).** mp 131–132 °C; ^1H NMR (500 MHz, $CDCl_3$) δ 8.95 (s, 1H, ArH), 7.69–7.64 (m, 2H, ArH), 7.60 (d, J = 8.3 Hz, 1H, ArH), 7.33–7.30 (t, J = 7.5 Hz, 2H, ArH), 7.28–7.26 (d, J = 7.2 Hz, 2H, ArH), 7.23 (t, J = 7.3 Hz, 2H, ArH), 5.30 (br s, 1H, NH), 3.83 (quart, J = 6.6 Hz, 2H, CH_2N), 2.99 (t, J = 7.0 Hz, 2H, CH_2); ^{13}C NMR (125 MHz, $CDCl_3$) δ 162.0, 159.6, 152.2, 139.4, 134.1, 128.9, 128.6, 127.5, 126.4, 125.6, 122.5, 120.2, 42.7, 35.7; HRMS-EI (70 eV) m/z calcd for $C_{16}H_{16}N_3$ $[M + H]^+$ 250.1344, found 250.1346.

***N*-(3-Phenylpropyl)quinazolin-2-amine (3ak).** mp 83–84 °C ^1H NMR (500 MHz, $CDCl_3$) δ 8.95 (s, 1H, ArH), 7.68–7.64 (m, 2H, ArH), 7.58 (d, J = 8.3 Hz, 1H, ArH), 7.30–7.26 (m, 2H, ArH), 7.23–7.17 (m, 4H, ArH), 5.32 (br s, 1H, NH), 3.59 (quart, J = 6.7 Hz, 2H, CH_2N), 2.76 (t, J = 7.8 Hz, 2H, CH_2), 2.02 (quint, J = 7.4 Hz, 2H, CH_2); ^{13}C NMR (125 MHz, $CDCl_3$) δ 161.9, 159.8, 152.2, 141.7, 134.1, 128.4, 128.4, 127.5, 125.9, 125.6, 122.4, 120.2, 41.1, 33.2, 31.2; HRMS-EI (70 eV) m/z calcd for $C_{17}H_{18}N_3$ $[M + H]^+$ 264.1501, found 264.1502.

***N*-Benzylquinazolin-2-amine (3al).** mp 123–125 °C ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.95 (s, 1H, ArH), 7.72–7.66 (m, 2H, ArH), 7.62 (t, J = 7.0 Hz, 1H, ArH), 7.42 (d, J = 7.4Hz, 2H, ArH), 7.35 (t, J = 7.4 Hz, 2H, ArH), 7.30–7.26 (m, 2H, ArH), 5.82 (br s, 1H, NH), 4.79 (d, J = 5.3 Hz, 2H, CH_2N); ^{13}C NMR (125 MHz, $CDCl_3$) δ 162.0, 159.6, 152.2, 139.2, 134.2, 128.6, 127.8, 127.5, 127.2, 125.6, 122.6, 120.3, 45.6.

***N*-(4-Methylbenzyl)quinazolin-2-amine (3am).** mp 142–143 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.93 (s, 1H, ArH), 7.70–7.65 (m, 2H, ArH), 7.61 (d, J = 8.3Hz, 1H, ArH), 7.30 (d, J = 7.7 Hz, 1H, ArH), 7.24 (t, J = 7.6 Hz, 2H, ArH), 7.15 (d, J = 7.9 Hz, 2H, ArH), 5.74 (br s, 1H, NH), 4.73 (d, J = 5.7 Hz, 2H, CH_2N), 2.34 (s, 3H, CH_3); ^{13}C NMR (125 MHz, $CDCl_3$) δ 162.1, 159.4, 152.1, 136.8, 136.0, 134.2, 129.2, 127.8, 127.5, 125.6, 122.6, 120.3, 45.7, 21.3; HRMS-EI (70 eV) m/z calcd for $C_{16}H_{16}N_3$ $[M + H]^+$ 250.1344, found 250.1349.

***N*-(4-(Trifluoromethyl)benzyl)quinazolin-2-amine (3an).** mp 152–153 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.96 (s, 1H, ArH), 7.71–7.67 (m, 2H, ArH), 7.60–7.58 (m, 3H, ArH), 7.52 (d, J = 8.1 Hz, 2H, ArH), 7.26 (t, J = 7.5 Hz, 1H, ArH), 5.82 (br s, 1H, NH), 4.85 (d, J = 6.3 Hz, 1H, CH_2N); ^{13}C NMR (125 MHz, $CDCl_3$) δ 162.1, 159.4, 152.0, 143.6, 134.3, 129.5 (quart, J_{C-F} = 29.2 Hz), 127.8, 127.5, 125.7, 125.5, 124.2 (quart, J_{C-F} = 270.8 Hz), 122.9, 120.5, 45,1; HRMS-EI (70 eV) m/z calcd for $C_{16}H_{13}N_3F_3$ $[M + H]^+$ 304.1062 found 304.1072.

***N*-(Thiophen-2-ylmethyl)quinazolin-2-amine (3ao).** mp 136–138 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.94 (s, 1H, ArH), 7.71–7.63 (m, 3H, ArH), 7.26 (t, J = 7.6 Hz, 1H, ArH), 7.20 (d, J = 5.0 Hz, 1H, ArH), 7.07 (d, J = 2.9 Hz, 1H, ArH), 6.96 (t, J = 4.3 Hz, 1H, ArH), 5.79 (br s, 1H, NH), 4.94 (d, J = 6.0 Hz, 2H, CH_2N); ^{13}C NMR (125 MHz, $CDCl_3$) δ 162.0, 159.1, 152.0, 142.1, 134.2, 127.6, 126.7, 125.7, 125.6, 124.9, 122.8, 120.4, 40.6; HRMS-EI (70 eV) m/z calcd for $C_{13}H_{12}N_3S$ $[M + H]^+$ 242.0752 found 242.0753.

***N*-Butyl-6-methoxyquinazolin-2-amine (3ba).** mp 86–87 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.88 (s, 1H, ArH), 7.53 (d, J = 9.1 Hz, 1H, ArH),7.35 (dd, J = 9.3 Hz and 2.7 Hz, 1H, ArH), 6.96 (d, J = 2.6 Hz, 1H, ArH), 5.11 (br s, 1H, NH), 3.86 (s, 3H, OCH_3), 3.52 (quart, J = 6.6 Hz, 2H, CH_2N), 1.65 (quint, J = 7.3 Hz, 2H, CH_2), 1.46 (sext, J = 7.4Hz, 2H, CH_2), 0.97 (t, J = 7.3 Hz, 3H, CH_3); ^{13}C NMR (125 MHz, $CDCl_3$) δ 160.3, 159.1, 154.8, 148.2, 127.1, 126.5, 120.2, 105.1, 55.5, 41.4, 31.8, 20.2, 13.8; HRMS-EI (70 eV) m/z calcd for $C_{13}H_{18}N_3O$ $[M + H]^+$ 230.1657, found 230.1654.

***N*-Butyl-6-(trifluoromethyl)quinazolin-2-amine (3ca).** mp 104–106 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.00 (s, 1H, ArH), 7.93 (s, 1H, ArH), 7.81 (dd, J = 8.8 Hz and 1.9 Hz, 1H, ArH), 7.65 (s, 1H, ArH), 5.49 (br s, 1H, NH), 3.56 (quart, J = 6.6 Hz, 2H, CH_2N), 1.67 (quint, J = 7.4 Hz, 2H, CH_2), 1.46 (sext, J = 7.4 Hz, 2H, CH_2), 0.98 (t, J = 7.4 Hz, 3H, CH_3); ^{13}C NMR (125 MHz, $CDCl_3$) δ 162.5, 160.6, 153.8, 129.7, 126.6, 125.5, 124.1 (quart, J_{C-F} = 33.3 Hz), 124.1 (quart, J_{C-F} = 270.8Hz), 118.8, 41.3, 31.5, 20.1, 13.8; HRMS-EI (70 eV) m/z calcd for $C_{13}H_{15}N_3F_3$ $[M + H]^+$ 270.1218, found 270.1219.

***N*-Butyl-6-fluoroquinazolin-2-amine (3da).** mp 83–84 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.91 (s, 1H, ArH), 7.59 (dd, J = 9.2 Hz and 5.1 Hz, 1H, ArH), 7.44 (dt, J = 8.9 Hz and 2.9 Hz, 1H, ArH), 7.27 (dd, J = 8.2 Hz and 2.9 Hz, 1H, ArH), 5.26 (br s, 1H, NH), 3.52 (quart, J = 6.6 Hz, 2H, CH_2N), 1.65 (quint, J = 7.3 Hz, 2H, CH_2), 1.46 (sext, J = 7.5 Hz, 2H, CH_2), 0.97 (t, J = 7.4 Hz, 3H, CH_3); ^{13}C NMR (125 MHz, $CDCl_3$) δ 161.0 (d, J_{C-F} = 4.5 Hz), 159.6, 157.6 (d, J_{C-F} = 242.7 Hz), 149.3, 127.8 (d, J_{C-F} = 7.8 Hz), 124.0 (d, J_{C-F} = 25.2 Hz), 119.7 (d, J_{C-F} = 8.2 Hz), 110.5 (d, J_{C-F} = 21.6 Hz), 41.4, 31.7, 20.2, 13.8; HRMS-EI (70 eV) m/z calcd for $C_{12}H_{15}N_3F$ $[M + H]^+$ 220.1250, found 220.1255.

6-Bromo-*N*-butylquinazolin-2-amine (3ea). mp 123–124 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.87 (s, 1H, ArH), 7.78 (d, J = 7.2 Hz, 1H, ArH), 7.70 (dd, J = 9.1 Hz and 2.2 Hz, 1H, ArH), 7.46 (d, J = 9.0 Hz, 1H, ArH), 5.32 (brs, 1H, NH), 3.52 (quart, J = 6.6 Hz,2H, CH_2N), 1.67 (quint, J = 8.1 Hz, 2H, CH_2), 1.45 (sext, J = 7.4 Hz, 2H, CH_2), 0.97 (t, J = 7.2 Hz, 3H, CH_3); ^{13}C NMR (125 MHz, $CDCl_3$) δ 160.9, 159.8, 151.2, 137.3, 129.5, 127.5, 121.1, 114.9, 41.6, 31.8, 20.3, 13.9; HRMS-EI (70 eV) m/z calcd for $C_{12}H_{15}N_3Br$ $[M + H]^+$ 280.0449, found 280.0454.

***N*-Butyl-4-phenylquinazolin-2-amine (3fa).** mp 72–74 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.78 (d, J = 8.6 Hz, 1H, ArH), 7.70–7.63 (m, 4H, ArH), 7.56–7.52 (m, 3H, ArH), 7.16–7.13 (m, 1H, ArH), 5.29 (br s, 1H, NH), 3.57 (quart, 2H, J = 6.6 Hz, CH_2N), 1.67 (quint, J = 7.2 Hz, 2H, CH_2),1.47 (sext, J = 7.5Hz, 2H, CH_2), 0.98 (t, J = 7.4 Hz, 3H, CH_3); ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.9, 159.1, 153.4, 137.5, 133.6, 129.6, 129.4, 128.4, 127.4, 126.1, 122.1, 118.4, 41.3, 31.8, 20.1, 13.9; HRMS-EI (70 eV) m/z calcd for $C_{18}H_{20}N_3$ $[M + H]^+$ 278.1657, found 278.1661.

***N*-Butylpyrimidin-2-amine (3ga) (ref. 15).** Oil, ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.26 (d, J = 4.5 Hz, 2H, CH, ArH), 6.48 (t, J = 4.8 Hz, 1H, ArH), 5.62 (br s, 1H, NH), 3.40 (quart, J = 6.6 Hz, 2H, CH_2N), 1.60 (quint, J = 7.4 Hz, 2H, CH_2), 1.42 (sext, J = 7.5 Hz, 2H, CH_2), 0.94 (t, J = 7.4 Hz, 3H, CH_3); ^{13}C NMR (125 MHz, $CDCl_3$) δ 162.5, 158.0, 110.2, 41.1, 31.6, 20.1, 13.7.

N-Butyl-5-phenylpyrimidin-2-amine (3ha). mp 88–90 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.52 (s, 2H, ArH), 7.47 (d, J = 7.3 Hz, 2H, ArH), 7.44 (t, J = 7.6 Hz, 2H, ArH), 7.34 (t, J = 7.2 Hz, 1H, ArH), 5.25 (br s, 1H, NH), 3.46 (quart, J = 6.6 Hz, 2H, CH_2N), 1.63 (quint, J = 7.4 Hz, 2H, CH_2), 1.45 (sext, J = 7.5 Hz, 2H, CH_2), 0.97 (t, J = 7.4 Hz, 3H, CH_3); ^{13}C NMR (125 MHz, $CDCl_3$) δ 161.9, 156.3, 135.7, 129.1, 127.2, 125.8, 123.6, 41.4, 31.9, 20.2, 13.7; HRMS-EI (70 eV) m/z calcd for $C_{14}H_{18}N_3$ $[M + H]^+$ 228.1501, found 228.1502.

***N*-Butyl-5-phenoxypyrimidin-2-amine (3ia).** mp 43–44 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.14 (s, 2H, ArH), 7.31 (t, J = 7.5 Hz, 2H, ArH), 7.06 (t, J = 7.2 Hz, 1H, ArH), 6.93 (d, J = 7.6 Hz, 2H, ArH), 5.12 (br s, 1H, NH), 3.40 (quart, J = 6.7 Hz, 2H, CH_2N), 1.61 (quint, J = 7.4 Hz, 2H, CH_2), 1.43 (sext, J = 7.4 Hz, 2H, CH_2), 0.96 (t, J = 7.4 Hz, 3H, CH_3); ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.7, 158.5, 151.0, 142.6, 130.0, 122.9, 116.5,41.6, 31.7, 20.2, 13.7; HRMS-EI (70 eV) m/z calcd for $C_{14}H_{18}N_3O$ $[M + H]^+$ 244.1450, found 244.1452.

***N*-Butyl-4,6-diphenylpyrimidin-2-amine (3ja) (ref. 16).** mp 75–76 °C (lit.[16] mp 65–66 °C); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.09–8.08 (m, 4H, ArH), 7.51–7.47(m, 6H, ArH), 7.39 (s, 1H, ArH), 5.25 (t, J = 5.4 Hz, 1H, NH), 3.60 (quart, J = 6.6 Hz, 2H, CH_2N), 1.68 (quint, J = 7.3 Hz, 2H, CH_2), 1.48 (sext, J = 7.4 Hz, 2H, CH_2),

0.99 (t, J = 7.4 Hz, 3H, CH_3); ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.7, 163.1, 138.2, 130.2, 128.7, 127.1, 102.8, 41.3, 32.0, 20.2, 13.9.

2-(butylamino)-6-phenylpyrimidin-4-ol (3ka) (ref. 17). mp 166–168 °C (lit.[17] mp 180–181 °C); ^{1}H NMR (500 MHz, $CDCl_3$) δ 11.89 (br s, 1H, OH), 8.00–7.98 (m, 2H, ArH), 7.45–7.46 (m, 3H, ArH), 6.23 (s, 1H, ArH), 6.21 (br s, 1H, NH), 3.55 (quart, J = 6.5 Hz, 2H, CH_2N), 1.68 (quint, J = 7.3 Hz, 2H, CH_2), 1.48 (sext, J = 7.4 Hz, 2H, CH_2), 0.99 (t, J = 7.4 Hz, 3H, CH_3); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.2, 165.3, 154.4, 137.6, 130.3, 128.5, 127.1, 97.1, 40.7, 31.5, 20.1, 13.8.

***N*2,*N*4-dibenzylquinazoline-2,4-diamine (5) (ref. 18).** mp 148–149 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.43 (s, 1H, NH), 8.00 (d, J = 8.1 Hz, 1H, ArH), 7.47 (t, J = 7.5 Hz, 1H, ArH), 7.33–7.16 (m, 11H, ArH), 7.08 (br s, 1H, NH), 7.03 (t, J = 7.5 Hz, 1H, ArH), 4.70 (s, 2H, CH_2N), 4.50 (s, 2H, CH_2N); ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.9, 159.4, 152.1, 141.3, 139.9, 132.2, 128.2, 128.0, 127.4, 127.2, 126.6, 126.2, 124.7, 122.7, 120.0, 111.1, 43.9, 43.3.

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Notes and references

1 (*a*) B. Herberich, G. Q. Cao, P. P. Chakrabarti, J. R. Falsey, L. Pettus, R. M. Rzasa, A. B. Reed, A. Reichelt, K. Sham, M. Thaman, R. P. Wurz, S. Xu, D. Zhang, F. Hsieh, M. R. Lee, R. V. Li, D. Grosfeld, M. H. Plant, B. Henkle, L. Sherman, S. Middleton, L. M. Wong and A. S. Tasker, *J. Med. Chem.*, 2008, **51**, 6271–6279; (*b*) E. F. DiMauro, J. Newcomb, J. J. Nunes, J. E. Bemis, C. Boucher, J. L. Buchanan, W. H. Buckner, V. J. Cee, L. Chai, H. L. Deak, L. F. Epstein, T. Faust, P. Gallant, S. D. Geuns-Meyer, A. Gore, Y. Gu, B. Henkle, B. L. Hodous, F. Hsieh, X. Huang, J. L. Kim, J. H. Lee, M. W. Martin, C. E. Masse, D. C. McGowan, D. Metz, D. Mohn, K. A. Morgenstern, A. Oliveira-dos-Santos, V. F. Patel, D. Powers, P. E. Rose, S. Schneider, S. A. Tomlinson, Y. Y. Tudor, S. M. Turci, A. A. Welcher, R. D. White, H. Zhao, L. Zhu and X. Zhu, *J. Med. Chem.*, 2006, **49**, 5671–5686; (*c*) C. D. Cox, M. J. Breslin, D. B. Whitman, J. D. Schreier, G. B. McGaughey, M. J. Bogusky, A. J. Roecker, S. P. Mercer, R. A. Bednar, W. Lemaire, J. G. Bruno, D. R. Reiss, C. M. Harrell, K. L. Murphy, S. L. Garson, S. M. Doran, T. Prueksaritanont, W. B. Anderson, C. Tang, S. Roller, T. D. Cabalu, D. Cui, G. D. Hartman, S. D. Young, K. S. Koblan, C. J. Winrow, J. J. Renger and P. J. Coleman, *J. Med. Chem.*, 2010, **53**, 5320–5332; (*d*) G. Traquandi, M. Ciomei, D. Ballinari, E. Casale, N. Colombo, V. Croci, F. Fiorentini, A. Isacchi, A. Longo, C. Mercurio, A. Panzeri, W. Pastori, P. Pevarello, D. Volpi, P. Roussel, A. Vulpetti and M. G. Brasca, *J. Med. Chem.*, 2010, **53**, 2171–2187; (*e*) N. J. Liverton, R. A. Bednar, B. Bednar, J. W. Butcher, C. F. Claiborne, D. A. Claremon, M. Cunningham, A. G. DiLella, S. L. Gaul, B. E. Libby, E. A. Lyle, J. J. Lynch, J. A. McCauley, S. D. Mosser, K. T. Nguyen, G. L. Stump, H. Sun, H. Wang, J. Yergey and K. S. Koblan, *J. Med. Chem.*, 2007, **50**, 807–819; (*f*) R. L. Thurmond and S. A. Wadsworth, *WO*2009/152287, Dec. 17, 2009.

2 (*a*) L. Wilson, *Org. Lett.*, 2001, **3**, 585–587; (*b*) J. Debray, J. M. Leveque, C. Philouze, M. Draye and M. Demeunynck, *J. Org. Chem.*, 2010, **75**, 2092–2095.

3 (*a*) D. J. Browns and B. T. England, *Aust. J. Chem.*, 1968, **21**, 2813–2818; (*b*) V. Martinez-Barrasa, F. Delgado, C. Burgos, J. L. Garcia-Navio, M. L. Izquierdo and J. Alvarez-Builla, *Tetrahedron*, 2000, **56**, 2481–2490; (*c*) M. Bi, G. Li, J. Hua, Y. Lin, J. Cao, Z. Shi and S. Feng, *Eur. J. Inorg. Chem.*, 2008, 1035–1038; (*d*) M. Bakherad, A. Keivanloo, Z. Kalantar and S. Jajarmi, *Tetrahedron Lett.*, 2011, **52**, 228–230.

4 For selected reviews, see: (*a*) M. H. S. A. Hamid, P. A. Slatford and J. M. J. Williams, *Adv. Synth. Catal.*, 2007, **349**, 1555–1575; (*b*) T. D. Nixon, M. K. Whittlesey and J. M. J. Williams, *Dalton Trans.*, 2009, 753–765; (*c*) G. E. Dobereiner and R. H. Grabtree, *Chem. Rev.*, 2010, **110**, 681–703; (*d*) G. Guillena, D. Ramon and M. Yus, *Chem. Rev.*, 2010, **110**, 1611–1641; (*e*) T. Suzuki, *Chem. Rev.*, 2011, **111**, 1825–1845; (*f*) S. Bahn, S. Imm, L. Neubert, M. Zhang, H. Neumann and M. Beller, *ChemCatChem*, 2011, **3**, 1853–1864; (*g*) A. C. Marr, *Catal. Sci. Technol.*, 2012, **2**, 279–287.

5 For selected examples, see: (*a*) K. Fujita, K. Yamamoto and R. Yamaguchi, *Org. Lett.*, 2002, **4**, 2691–2694; (*b*) K. Fujita, Z. Li, N. Ozeki and R. Yamaguchi, *Tetrahedron Lett.*, 2003, **44**, 2687–2690; (*c*) K. Fujita, T. Fujii and R. Yamaguchi, *Org. Lett.*, 2004, **6**, 3525–3528; (*d*) S. Whitney, R. Grigg, A. Derrick and A. Keep, *Org. Lett.*, 2007, **9**, 3299–3302; (*e*) K. Fujita, Y. Enoki and R. Yamaguchi, *Tetrahedron*, 2008, **64**, 1943–1954; (*f*) A. Prades, R. Corberán, M. Poyatos and E. Peris, *Chem.–Eur. J.*, 2008, **14**, 11474–11479; (*g*) R. Yamaguchi, S. Kawagoe, C. Asai and K. Fujita, *Org. Lett.*, 2008, **10**, 181–184; (*h*) B. Blank, S. Michlik and R. Kempe, *Chem.–Eur. J.*, 2009, **15**, 3790–3799; (*i*) D. Gnanamgari, E. L. O. Sauer, N. D. Schley, C. Butler, C. D. Incarvito and R. H. Crabtree, *Organometallics*, 2009, **28**, 321–325; (*j*) O. Saidi, A. J. Blacker, M. M. Farah, S. P. Marsden and J. M. J. Williams, *Chem. Commun.*, 2010, **46**, 1541–1543; (*k*) M. Tursky, L. L. R. Lorentz-Petersen, L. B. Olsen and R. Madsen, *Org. Biomol. Chem.*, 2010, **8**, 5576–5582; (*l*) M. Zhu, K. Fujita and R. Yamaguchi, *Org. Lett.*, 2010, **12**, 1336–1339; (*m*) S. Michlik and R. Kempe, *Chem.–Eur. J.*, 2010, **16**, 13193–13198; (*n*) N. Andrushko, V. Andrushko, P. Roose, K. Moonen and A. Boner, *ChemCatChem*, 2010, **2**, 640–643; (*o*) R. Kawahara, K. Fujita and R. Yamaguchi, *Adv. Synth. Catal.*, 2011, **353**, 1161–1168; (*p*) I. Cumpstey, S. Agrawal, K. E. Borbasa and B. Martin-Matute, *Chem. Commun.*, 2011, **47**, 7827–7829; (*q*) M. A. Berliner, S. P. A. Dubant, T. Makowski, K. Ng, B. Sitter, C. Wager and

Y. Zhang, *Org. Process Res. Dev.*, 2011, **15**, 1052–1062; (*r*) S. Bhat and V. Sridharan, *Chem. Commun.*, 2012, **48**, 4701–4703.

6 For selected examples, see: (*a*) M. H. S. A. Hamid and J. M. J. Williams, *Chem. Commun.*, 2007, 725–727; (*b*) C. Gunanathan and D. Milstein, *Angew. Chem., Int. Ed.*, 2008, **47**, 8661–8664; (*c*) H. S. A. Hamid, C. L. Allen, G. W. Lamb, A. C. Maxwell, H. C. Maytum, A. J. A. Watson and J. M. J. Williams, *J. Am. Chem. Soc.*, 2009, **131**, 1766–1774; (*d*) S. Bahn, A. Tillack, S. Imm, K. Mevius, D. Michalik, D. Hollmann, L. Neubert and M. Beller, *ChemSusChem*, 2009, **2**, 551–557; (*e*) J. He, J. W. Kim, K. Yamaguchi and N. Mizuno, *Angew. Chem., Int. Ed.*, 2009, **48**, 9888–9891; (*f*) K. Yamaguchi, J. He, T. Oishi and N. Mizuno, *Chem.–Eur. J.*, 2010, **16**, 7199–7207; (*g*) S. Bahn, S. Imm, K. Mevius, L. Neubert, A. Tillack, J. M. J. Williams and M. Beller, *Chem.–Eur. J.*, 2010, **16**, 3590–3593; (*h*) B. Sundararaju, Z. Tang, M. Achard, G. V. M. Sharma, L. Toupet and C. Bruneau, *Adv. Synth. Catal.*, 2010, **352**, 3141–3146; (*i*) S. Imm, S. Bahn, M. Zhang, L. Neubert, H. Neumann, F. Klasovsky, J. Pfeffer, T. Haas and M. Beller, *Angew. Chem., Int. Ed.*, 2011, **50**, 7599–7603; (*j*) M. Zhang, S. Imm, S. Bahn, H. Neumann and M. Beller, *Angew. Chem., Int. Ed.*, 2011, **50**, 11197–11201; (*k*) Z. Sahli, B. Sundararaju, M. Achard and C. Bruneau, *Org. Lett.*, 2011, **13**, 3964–3967; (*l*) A. J. A. Watson, A. C. Maxwell and J. M. J. Williams, *J. Org. Chem.*, 2011, **76**, 2328–2331; (*m*) R. Cano, D. J. Ramón and M. Yus, *J. Org. Chem.*, 2011, **76**, 5547–5557; (*n*) S. Agrawal, M. Lenormand and B. Martin-Matute, *Org. Lett.*, 2012, **14**, 1456–1459.

7 For selected examples, see: (*a*) F. Shi, M. K. Tse, X. Cui, D. Gordes, D. Michalik, T. Y. Deng and M. Beller, *Angew. Chem., Int. Ed.*, 2009, **48**, 5912–5915; (*b*) K. Shimizu, M. Nishimura and A. Satsuma, *ChemCatChem*, 2009, **1**, 497–503; (*c*) A. Martinez-Asencio, M. Yus and D. J. Ramon, *Synthesis*, 2011, 3730–3740; (*d*) W. He, L. Wang, C. Sun, K. Wu, S. He, J. Chen, P. Wu and Z. Yu, *Chem.–Eur. J.*, 2011, **17**, 13308–13317; (*e*) X. Yu, C. Liu, L. Jiang and Q. Xu, *Org. Lett.*, 2011, **13**, 6184–6187; (*f*) L. He, Y. Qian, R. Ding, Y. Liu, H. He, K. Fan and Y. Cao, *ChemSusChem*, 2012, **5**, 621–624.

8 (*a*) F. Li, H. Shan, Q. Kang and L. Chen, *Chem. Commun.*, 2011, **47**, 5058–5060; (*b*) F. Li, H. Shan, L. Chen, Q. Kang and P. Zou, *Chem. Commun.*, 2012, **48**, 603–605; (*c*) F. Li, Q. Kang, H. Shan, L. Chen and J. Xie, *Eur. J. Org. Chem.*, 2012, 5085–5092.

9 F. Li, C. Sun, H. Shan, X. Zou and J. Xie, *ChemCatChem*, DOI: 10.1002/cctc.201200648.

10 Fujita, Yamaguchi and co-workers revealed the catalytic activity of $[Cp^*IrCl_2]_2$ toward oxidation of alcohols to the corresponding aldehydes, see: K. Fujita, S. Furukawa and R. Yamaguchi, *J. Organomet. Chem.*, 2002, **649**, 289–292.

11 Bergman and co-workers demonstrated the amido–alkoxo exchange reaction for Cp*Ir complexes, see: D. S. Glueck, L. J. N. Winslow and R. G. Bergman, *Organometallics*, 1991, **10**, 1462–1479.

12 Fristrup, Madsen and co-workers have recently investigated in detail the mechanism for the iridium-catalyzed alkylation of amines with alcohols, see: P. Fristrup, M. Tursky and R. Madsen, *Org. Biomol. Chem.*, 2012, **10**, 2569–2577.

13 H. Mili and J. Yamada, *Chem. Pharm. Bull.*, 1982, **30**, 2313–2318.

14 L. Huang, S. Liu, E. A. Lunney and S. P. Planken, *US*7998978, 2007.

15 A. R. Katritzky, S. Rachwal and B. Rachwal, *J. Chem. Soc., Perkin Trans. 1*, 1987, 805–809.

16 S. Goswami, A. Hazra and S. Jana, *Bull. Chem. Soc. Jpn.*, 2009, **82**, 1175–1181.

17 D. Font, M. Heras and J. M. Villalgordo, *Synthesis*, 2002, 1833–1842.

18 R. J. Deshaies, T. F. Chou, F. J. Schoenen, K. Li, K. J. Frankowski, J. Aube, S. W. Gerritz and H. J. Zhou, *WO*2011140527, 2011.