


 Cite this: *RSC Adv.*, 2021, **11**, 3477

 Received 25th November 2020
 Accepted 4th January 2021

 DOI: 10.1039/d0ra09994e
rsc.li/rsc-advances

An efficient synthesis of 4-phenoxy-quinazoline, 2-phenoxy-quinoxaline, and 2-phenoxy-pyridine derivatives using aryne chemistry†

 Mahesh K. Zilla,^{‡ab} Sheena Mahajan,^{‡b} Rajni Khajuria,^c Vivek K. Gupta,^d Kamal K. Kapoor^e and Asif Ali^{*bf}

Herein we report the mild and efficient synthesis of 4-phenoxyquinazoline, 2-phenoxyquinoxaline, and 2-phenoxypyridine derivatives from the starting materials *viz.* quinazolin-4(3*H*)-one, quinoxalin-2(1*H*)-one, and pyridin-2(1*H*)-one and aryne generated *in situ* from 2-(trimethylsilyl)phenyl trifluoromethanesulfonate and cesium fluoride. This synthetic methodology gives a new environmentally benign way for the preparation of several unnatural series of 4-phenoxyquinazoline, 2-phenoxyquinoxaline and 2-phenoxypyridine compounds with high yields and broad substrate scope.

Introduction

Aryne intermediates are one of the most important classes of organic species and are useful as substrates in various reactions for developing new synthetic methodologies,¹ preparing heterocyclic molecules² and in the total synthesis of natural products.³ Although aryne was generated from different starting materials, among all the reported methods, generation of aryne developed using the Kobayashi *et al.*⁴ method from trimethylsilyl phenyl triflate and cesium fluoride has been widely used for the last two decades because of its easy formation *in situ* and generation under normal conditions. Due to the highly electrophilic nature of arynes,⁵ these readily participated in reactions with the reactants and gave addition,⁶ insertion type products with good yields and atom economy.⁷ Because of their high reactivity in the reactions, arynes readily participate in reactions with substrates like styrenes without the use of any catalyst.⁸ After reading several reviews published by top authors

on aryne chemistry,⁹ the main focus of the present work is the development of a mild, simple, eco-benign methodology using aryne chemistry with heterocyclic compounds.

Literature reports reveals very few reactions of arynes with amides. Pintori *et al.*¹⁰ reported the insertion of benzene ring into the amide bond by using aryne chemistry. Later on, facile *N*-arylation of acetanilides with arynes was reported by Haber *et al.*¹¹ Herein our method, we have got the result of aryl substituted iminoxy derivatives on amide group containing heterocyclic compounds (Scheme 1).

Heterocyclic compounds have unique importance in organic synthesis and in biological activity. Among these quinazolines, quinoxalines are the important class of building blocks found in a variety of pharmaceuticals. Quinazolines are the

^aDepartment of Chemical Sciences, Indian Institute of Science Education and Research (IISER), Berhampur, Odisha 760010, India. E-mail: mzilla@iiserbpr.ac.in

^bCSIR-Indian Institute of Integrative Medicine, Canal Road, Jammu-180001, India. E-mail: sheena01mahajan@gmail.com

^cDepartment of Chemistry, GDC for Women Kathua, Kathua-184101, India. E-mail: khajuriarajni36@gmail.com

^dPost-Graduate Department of Physics & Electronics, University of Jammu, Jammu Tawi-180006, India. E-mail: vivek.gupta2k9@gmail.com

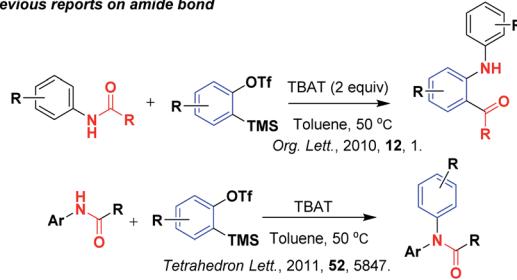
^eDepartment of Chemistry, University of Jammu, Jammu Tawi-180006, India. E-mail: kamalka@gmail.com

^fCSIR-Traditional Knowledge Digital Library (TKDL), 14-Satsang Vihar, Vigyan Suchna Bhawan, New Delhi-110067, India. E-mail: asifali@csir.res.in

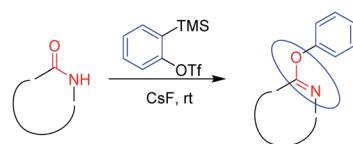
† Electronic supplementary information (ESI) available: ¹H, ¹³C NMR, other spectra of all the compounds and crystal data of **8c** & **8e**. CCDC 1451640 and 1451639. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/d0ra09994e

‡ Mahesh K. Zilla and Sheena Mahajan have equally contributed as a first author.

Previous reports on amide bond



Present work on amide bond



Scheme 1 Reactions of arynes with amides.



compounds showing different medicinal properties such as anti-convulsant,¹² anti-bacterial,¹³ anti-diabetic,¹⁴ anti-carcinogen¹⁵ etc., whereas quinoxalines are having anti-biotic,¹⁶ anti-mycobacterial,¹⁷ anti-viral,¹⁸ anti-osteoclast,¹⁹ anti-convulsant²⁰ properties. Some of the important biologically active quinazoline and quinoxaline derivatives are shown in Fig. 1.

When we processed the work on developing mild and simple synthetic methodologies with aryne, we got an unfortunate result of aryl substituted iminoxy quinazoline of unnatural compound with an appropriate yield which would be useful for the preparation of a series of compounds in efficient manner. So the main objective of the present methodology was the diversification in preparation of unnatural heterocyclic compounds.

Results and discussion

We commenced our investigation using 2-phenylquinazolin-4(3H)-one **1a** and readily available 2-(trimethylsilyl)phenyl trifluoromethanesulfonate **2** (Table 1). When the reaction was performed with KF/18-crown-6 as the fluoride source for the generation of benzene from 2-(trimethylsilyl)phenyltrifluoromethane sulfonate **2** at room temperature in acetonitrile, desired product **3a** was obtained in a moderate yield of 45% (Table 1, entry 1). However by performing the same reaction with the increased amount of KF/18-crown-6 and KF/18-crown-6, minor effect in the product **3a** yield *i.e.* 48% (Table 1, entry 2) was observed. Also by changing the solvent of the reaction as DME, poor yield of the desired product **3a** (Table 1, entry 3) was obtained. Further, with different fluoride sources such as TBAF, TBAT the product **3a** in moderate yields of 55% and 48% was obtained. Further, by employing CsF as a fluoride source, product **3a** was obtained in high yield (72%). Later, by increasing the amount of CsF, to our delight, yield of the product **3a** increased to 89%. Also by carrying out the reaction in different solvents such as DCM, toluene, DME less yields of product was obtained (Table 1, entry 8, 9, 10). Thus, 1 mmol of 2-phenyl quinazolin-4(3H)-one **1a**, 1.2 mmol of 2-(trimethylsilyl)phenyl trifluoromethanesulfonate **2** in acetonitrile in presence

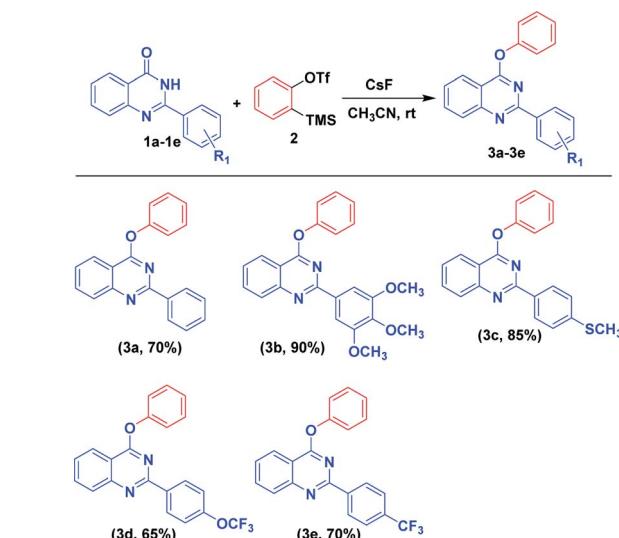
Table 1 Optimization reaction for the preparation of 4-phenoxy-2-phenylquinazoline **3a** from 2-phenylquinazolin-4(3H)-one **1a** with aryne^a

Entry	F ⁻ source	Equiv.	Solvent	Yield ^b (%)
1.	KF/18-crown-6	2.0	CH ₃ CN	45
2.	KF/18-crown-6	3.0	CH ₃ CN	48
3.	KF/18-crown-6	3.0	DME	22
4.	TBAF ^c	2.0	CH ₃ CN	55
5.	TBAT ^d	2.0	CH ₃ CN	48
6.	CsF	2.0	CH ₃ CN	72
7.	CsF	3.0	CH ₃ CN	89
8.	CsF	3.0	DCM	5
9.	CsF	3.0	Toluene	5
10.	CsF	3.0	DME	48

^a Reaction conditions (unless otherwise stated): **1a** (0.45 mmol, 1.0 equiv.), **2** (0.54 mmol, 1.2 equiv.), F⁻ source, solvent (8 mL), at room temperature for 4 h. ^b Isolated yield. ^c Tetrabutylammonium fluoride. ^d Tetrabutylammonium difluorotriphenylsilicate.

of 3 mmol of CsF at room temperature were the optimized reaction conditions.

With the optimized reaction conditions in hand, we examined the substrate scope with different substituted 2-phenylquinazolin-4(3H)-one derivatives, and the results are depicted in Scheme 2. With electron donating groups (OCH₃, SCH₃)



Scheme 2 Substrate scope of different substituted 2-phenylquinazolin-4(3H)-one derivatives with benzene^a. ^aReaction conditions (unless otherwise stated): **1a–e** (0.45 mmol, 1.0 equiv.), **2** (0.54 mmol, 1.2 equiv.), CsF (1.35 mmol, 3 equiv.), acetonitrile solvent (8 mL), at room temperature for 4–6 h.

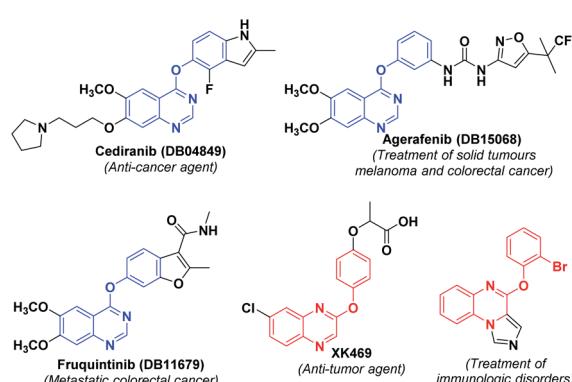


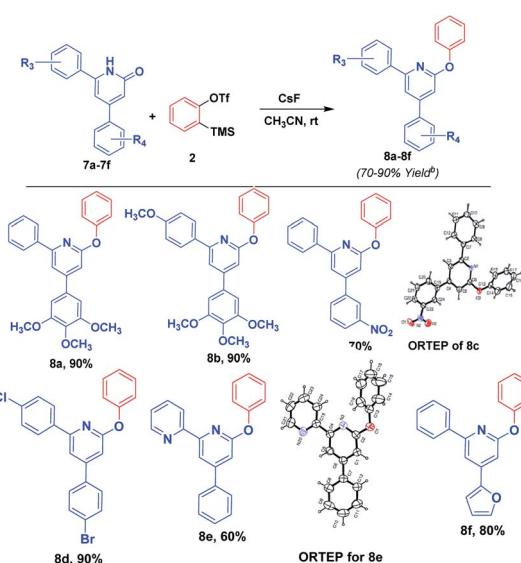
Fig. 1 Representative biologically active quinazolines and quinoxalines.



substituted on 2-phenylquinazolin-4(3*H*)-one, high yield of the desired product was obtained (Scheme 2: *ex. OCH₃, SCH₃*). Whereas with electron withdrawing groups, less yield of the desired product was obtained (Scheme 2: *ex. CF₃, OCF₃*).

Next, we extended to apply the same optimized reaction condition on quinoxalin-2(1*H*)-one derivatives which resulted in two different compounds *viz.* 2-phenoxyquinoxaline and 1-phenylquinoxalin-2(1*H*)-one in the ratio of 7 : 3. 2-Phenoxyquinoxaline was obtained as major product which was confirmed by the absence of carbonyl stretching peak in the IR spectrum indicated that it was arylated to iminoxy compound. Whereas the minor quantity compound, 1-phenylquinoxalin-2(1*H*)-one structure was confirmed by the IR spectrum having specific peak at 1663 cm⁻¹ for the carbonyl group of amide indicating that no change in the carbonyl of the amide group confirming the N-arylated product. Further, we have enlarged the work for different substituted quinoxalin-2(1*H*)-one derivatives and the results are shown in Scheme 3.

Further, we have applied the optimized reaction on the pyridin-2(1*H*)-ones, predominantly resulting 2-phenoxy pyridine derivatives in high yield. Although the reaction of pyridones with aryne was reported by Masayuki Kuzuva *et al.* in 1984, the authors have generated aryne from the anthranilic acid with the use of hazardous chemical isopentyl nitrile in a mixture of solvents acetone and chloroform at a temperature of 70 °C with moderate yield. Where as in our method, we have generated aryne from 2-(trimethylsilyl)phenyl trifluoromethanesulfonate with CsF at room temperature resulting in a high yield of product in an efficient manner. Further, we have applied this reaction to enlarge the substrate scope, and the results are mentioned in Scheme 4. Structure of product 8e was confirmed by X-ray crystallographic studies. An ORTEP view of the compound 8e with atomic labeling is shown in Scheme



Scheme 4 Application of the optimized reaction condition on different substituted pyridine-2(1*H*)-one derivatives with benzene^a. ^aReaction conditions (unless otherwise stated): 7a–f (0.24 mmol, 1.0 equiv.), 2 (0.29 mmol, 1.2 equiv.), CsF (0.72 mmol, 3 equiv.), acetonitrile solvent (8 mL), at room temperature for 4–6 h. ^bIsolated yield.

4.²¹ The geometry of the molecule was calculated using the WinGX,²² PARST²³ and PLATON²⁴ softwares. The crystallographic data is summarized in ESI.†

Experimental

Materials and methods

All the experiments were performed in an oven dried glass apparatus. All the commercially available reagents were purchased from Aldrich and were used without further purification. Melting points (°C) were measured in open glass capillaries using Perfit melting point apparatus and are uncorrected. The progress of reaction was monitored by thin layer chromatography (TLC) using silica gel pre-coated aluminium sheets (60 F254, Merck). Visualization of spots was effected by exposure to ultraviolet light (UV) at 365 nm and 254 nm, iodine vapours and 2% 2,4-dinitrophenylhydrazine in methanol containing few drops of H₂SO₄, dragendorff reagent and anisaldehyde reagent. Solvents used in purification were distilled before use. Recrystallization was achieved with ethanol. IR spectra (ν , cm⁻¹) were recorded on Perkin-Elmer FTIR spectrophotometer using KBr discs. ¹H and ¹³C NMR were recorded on Bruker AC-400 spectrometer operating at 400 MHz for ¹H and 100 MHz for ¹³C with tetramethylsilane (TMS) as an internal standard. The chemical shifts are expressed in δ (ppm) downfield from TMS. All the ¹³C NMR spectra are proton decoupled. J values are given in Hertz (Hz). The abbreviations s, d, dd, t, q and m in ¹H NMR spectra refer to singlet, doublet, doublet of doublet, triplet, quartet and multiplet respectively. Solvents were removed using Heidolph rotary evaporator. Electrospray ionization mass spectra MS (ESI) were recorded on Micro Mass VG-7070 H mass spectrometer at



S. No.	Entry	Substituent (R ₂ -X)	Products yield/Ratio 5a-5e:6a-6e
$R_2 =$			
1.	4a	X = -p-OCH ₃	90% / 7:3
2.	4b	X = -3,4,5-OCH ₃	95% / 7:3
3.	4c	X = -3,4-OCH ₂ O	85% / 7:3
4.	4d	X = -p-CF ₃	70% / 7:3
5.	4e	X = -o-Cl	70% / 7:3

Scheme 3 Application of the optimized reaction condition on different substituted (E)-3-styrylquinoxalin-2(1*H*)-one derivatives with benzene^a. ^aReaction conditions (unless otherwise stated): 4a–e (0.28 mmol, 1.0 equiv.), 2 (0.33 mmol, 1.2 equiv.), CsF (0.84 mmol, 3 equiv.), acetonitrile solvent (8 mL), at room temperature for 4–6 h. ^bIsolated yield.



70 eV. Elemental analysis was performed on Leco CHNS-932 analyzer.

Crystal structure determination and refinement for 4-(3-nitrophe-nyl)-2-phenoxy-6-phenylpyridine (8c)

X-ray intensity data of 7234 reflections (of which 3530 unique) were collected on X'calibur CCD area-detector diffractometer equipped with graphite monochromated MoK α radiation ($\lambda = 0.71073 \text{ \AA}$). The crystal used for data collection was of dimensions $0.30 \times 0.20 \times 0.20 \text{ mm}$. The cell dimensions were determined by least-squares fit of angular settings of 1788 reflections in the θ range 3.93 to 27.57° . The intensities were measured by ω scan mode for θ ranges 3.53 to 26.00° . 2176 reflections were treated as observed ($I > 2\sigma(I)$). Data were corrected for Lorentz, polarisation and absorption factors. The structure was solved by direct methods using SHELXS97.²⁵ Full-matrix least-squares refinement was carried out using SHELXL97.²⁵ The final refinement cycles converged to an $R = 0.0445$ and $wR(F^2) = 0.0911$ for the observed data. Residual electron densities ranged from $-0.126 < \Delta\rho < 0.158 \text{ e\AA}^{-3}$. Atomic scattering factors were taken from International Tables for X-ray Crystallography (1992, vol. C, Tables 4.2.6.8 and 6.1.1.4). The crystallographic data are summarized in ESI.†

Crystal structure determination and refinement for 6-phenoxy-4-phenyl-2,2'-bipyridine (8e)

X-ray intensity data of 5807 reflections (of which 3223 unique) were collected on X'calibur CCD area-detector diffractometer equipped with graphite monochromated MoK α radiation ($\lambda = 0.71073 \text{ \AA}$). The crystal used for data collection was of dimensions $0.30 \times 0.20 \times 0.20 \text{ mm}$. The cell dimensions were determined by least-squares fit of angular settings of 1471 reflections in the θ range 4.12 to 26.09° . The intensities were measured by ω scan mode for θ ranges 3.52 to 26.00° . 1919 reflections were treated as observed ($I > 2\sigma(I)$). Data were corrected for Lorentz, polarisation and absorption factors. The structure was solved by direct methods using SHELXS97.²⁵ All non-hydrogen atoms of the molecule were located in the best E-map. Full-matrix least-squares refinement was carried out using SHELXL97.²⁵ The final refinement cycles converged to an $R = 0.0533$ and $wR(F^2) = 0.1235$ for the observed data. Residual electron densities ranged from $-0.162 < \Delta\rho < 0.172 \text{ e\AA}^{-3}$. Atomic scattering factors were taken from International Tables for X-ray Crystallography (1992, vol. C, Tables 4.2.6.8 and 6.1.1.4). The crystallographic data are summarized in ESI.†

General procedure for the preparation of 4-phenoxy-2-arylquinazoline (3a–e) with aryne

To a stirred solution of 2-phenylquinazolin-4(3H)-one (1a–e) (0.45 mmol, 1.0 equiv.) and trimethylsilyl phenyl triflate (2) (0.54 mmol, 1.2 equiv.) in acetonitrile as solvent, was added cesium fluoride (1.35 mmol, 3.0 equiv.) at room temperature. The mixture was stirred at room temperature for 4 h, after completing the reaction, reaction mixture was concentrated *in vacuo*. To the resulting residue, water was added, and the mixture was extracted with ethyl acetate three times. The

combined organic phase was dried over sodium sulphate, and concentrated *in vacuo*. The crude product was purified by column chromatography (EtOAc in hexane) resulting the product.

4-Phenoxy-2-phenylquinazoline (3a). ^1H NMR (400 MHz, CDCl₃): δ 8.25 (d, $J = 7.7 \text{ Hz}$, 3H), 7.94 (d, $J = 8.4 \text{ Hz}$, 1H), 7.75 (dd, $J = 11.3$, 4.0 Hz, 1H), 7.47 (t, $J = 7.6 \text{ Hz}$, 1H), 7.39 (t, $J = 7.8 \text{ Hz}$, 2H), 7.26 (ddd, $J = 19.9$, 10.0, 4.5 Hz, 6H); ^{13}C NMR (101 MHz, CDCl₃) δ 167.51, 160.71, 153.53, 153.49, 138.51, 134.77, 131.38, 130.25, 129.28, 129.19, 128.97, 127.64, 126.35, 124.39, 122.85, 115.94; HRMS-ESI [M + H]⁺ *m/z* calcd for C₂₀H₁₅N₂O: 299.1179, found 299.1176.

4-Phenoxy-2-(3,4,5-trimethoxyphenyl)quinazoline (3b). ^1H NMR (400 MHz, CDCl₃): δ 8.25 (d, $J = 7.9 \text{ Hz}$, 1H), 7.95 (d, $J = 8.4 \text{ Hz}$, 1H), 7.79 (dd, $J = 11.2$, 4.1 Hz, 1H), 7.55 (s, 2H), 7.49 (t, $J = 7.5 \text{ Hz}$, 1H), 7.39 (t, $J = 7.8 \text{ Hz}$, 2H), 7.28 (d, $J = 7.7 \text{ Hz}$, 2H), 7.22 (t, $J = 7.3 \text{ Hz}$, 1H), 3.79 (s, 3H), 3.76 (s, 6H); ^{13}C NMR (101 MHz, CDCl₃): δ 166.61, 159.11, 153.07, 152.84, 152.74, 140.40, 133.97, 132.90, 129.21, 128.05, 126.74, 125.50, 123.53, 122.40, 114.81, 105.49, 60.88, 55.91; HRMS-ESI [M + H]⁺ *m/z* calcd for C₂₃H₂₁N₂O₄: 389.1496, found 389.1506.

2-(4-(Methylthio)phenyl)-4-phenoxyquinazoline (3c). ^1H NMR (400 MHz, CDCl₃): δ 8.41 (d, $J = 8.4 \text{ Hz}$, 2H), 8.03 (d, $J = 8.1 \text{ Hz}$, 1H), 7.86 (d, $J = 8.4 \text{ Hz}$, 1H), 7.70 (t, $J = 7.4 \text{ Hz}$, 1H), 7.43–7.29 (m, 5H), 7.28–7.17 (m, 3H), 4.15 (s, 3H); ^{13}C NMR (101 MHz, CDCl₃): δ 167.05, 159.44, 151.81, 139.46, 136.62, 134.81, 133.50, 132.00, 129.84, 129.34, 129.16, 127.92, 127.58, 126.43, 123.46, 115.29, 54.05; HRMS-ESI [M + H]⁺ *m/z* calcd for C₂₁H₁₇N₂OS: 355.1624, found 355.1628.

4-Phenoxy-2-(4-(trifluoromethoxy)phenyl)quinazoline (3d). ^1H NMR (400 MHz, CDCl₃): δ 8.24 (t, $J = 7.5 \text{ Hz}$, 3H), 7.91 (d, $J = 8.4 \text{ Hz}$, 1H), 7.76 (dd, $J = 11.2$, 4.0 Hz, 1H), 7.47 (t, $J = 7.5 \text{ Hz}$, 1H), 7.42–7.36 (m, 2H), 7.28–7.19 (m, 3H), 7.11 (d, $J = 8.5 \text{ Hz}$, 2H); ^{13}C NMR (101 MHz, CDCl₃): δ 166.83, 158.56, 152.66, 152.57, 151.07, 136.26, 134.10, 130.10, 129.51, 128.17, 127.09, 125.70, 123.62, 122.03, 120.47, 115.10; HRMS-ESI [M + H]⁺ *m/z* calcd for C₂₁H₁₄F₃N₂O₂: 383.1002, found 383.1004.

4-Phenoxy-2-(4-(trifluoromethyl)phenyl)quinazoline (3e). ^1H NMR (400 MHz, CDCl₃): δ 8.34 (d, $J = 8.1 \text{ Hz}$, 2H), 8.28 (d, $J = 8.1 \text{ Hz}$, 1H), 7.96 (d, $J = 8.4 \text{ Hz}$, 1H), 7.81 (t, $J = 7.7 \text{ Hz}$, 1H), 7.54 (t, $J = 7.8 \text{ Hz}$, 3H), 7.42 (t, $J = 7.8 \text{ Hz}$, 2H), 7.30–7.24 (m, 3H); ^{13}C NMR (101 MHz, CDCl₃): δ 167.76, 159.26, 153.46, 153.36, 141.82, 135.04, 130.35, 129.52, 129.15, 128.26, 126.58, 126.13, 126.10, 124.49, 122.83, 116.16; HRMS-ESI [M + H]⁺ *m/z* calcd for C₂₁H₁₄F₃N₂O: 367.1053, found 367.1055.

General procedure for the preparation of (E)-2-phenoxy-3-styrylquinoxaline (5a–e) with aryne

To a stirred solution of (E)-3-styrylquinoxalin-2(1H)-one (4a–e) (0.28 mmol, 1.0 equiv.) and trimethylsilyl phenyl triflate (2) (0.33 mmol, 1.2 equiv.) in acetonitrile as solvent, was added cesium fluoride (1.35 mmol, 3.0 equiv.) at room temperature. The mixture was stirred at room temperature for 4 h, after completing the reaction, reaction mixture was concentrated *in vacuo*. To the resulting residue, water was added, and the mixture was extracted with ethyl acetate three times. The



combined organic phase was dried over sodium sulphate, and concentrated *in vacuo*. The crude product was purified by column chromatography (EtoAc in hexane), resulting the product.

(E)-2-(4-Methoxystyryl)-3-phenoxyquinoxaline (5a). ^1H NMR (400 MHz, CDCl_3): δ 8.04 (d, $J = 16.0$ Hz, 1H), 7.96–7.91 (m, 1H), 7.62–7.54 (m, 4H), 7.52–7.44 (m, 2H), 7.40 (t, $J = 7.8$ Hz, 2H), 7.21 (dd, $J = 13.1, 11.1$ Hz, 3H), 6.86 (d, $J = 8.6$ Hz, 2H), 3.77 (s, 3H). ^{13}C NMR (101 MHz, CDCl_3): δ 160.58, 155.15, 153.11, 144.33, 139.95, 139.30, 137.27, 129.59, 129.37, 129.29, 129.04, 128.38, 127.52, 127.28, 125.28, 121.86, 118.65, 114.30, 55.38; HRMS-ESI [M + H]⁺ m/z calcd for $\text{C}_{23}\text{H}_{19}\text{N}_2\text{O}_2$: 355.1441, found 355.1447.

(E)-3-(4-Methoxystyryl)-1-phenylquinoxalin-2(1H)-one (6a). ^1H NMR (400 MHz, CDCl_3): δ 8.13 (d, $J = 16.2$ Hz, 1H), 7.84–7.78 (m, 1H), 7.59–7.45 (m, 6H), 7.28–7.16 (m, 4H), 6.84 (d, $J = 8.6$ Hz, 2H), 6.57 (d, $J = 8.1$ Hz, 1H), 3.76 (s, 3H). ^{13}C NMR (101 MHz, CDCl_3): δ 160.73, 154.93, 153.36, 138.57, 136.13, 133.64, 133.43, 130.31, 129.50, 129.41, 129.40, 129.32, 129.07, 128.30, 124.00, 120.27, 115.40, 114.31, 55.37; HRMS-ESI [M + H]⁺ m/z calcd for $\text{C}_{23}\text{H}_{19}\text{N}_2\text{O}_2$: 355.1441, found 355.1435.

(E)-2-Phenoxy-3-(3,4,5-trimethoxystyryl)quinoxaline (5b). ^1H NMR (400 MHz, CDCl_3): δ 8.11 (d, $J = 16.0$ Hz, 1H), 8.02 (dd, $J = 7.8, 1.7$ Hz, 1H), 7.70–7.62 (m, 2H), 7.57 (ddd, $J = 7.6, 5.2, 1.8$ Hz, 2H), 7.52–7.47 (m, 2H), 7.35–7.29 (m, 3H), 6.94 (s, 2H), 3.94 (s, 6H), 3.91 (s, 3H). ^{13}C NMR (126 MHz, CDCl_3): δ 155.25, 153.46, 152.99, 143.81, 139.87, 139.40, 139.22, 137.73, 132.13, 129.68, 129.37, 128.41, 127.65, 127.30, 125.45, 122.01, 120.37, 104.83, 61.04, 56.23; HRMS-ESI [M + H]⁺ m/z calcd for $\text{C}_{25}\text{H}_{23}\text{N}_2\text{O}_4$: 415.1652, found 415.1653.

(E)-1-Phenyl-3-(3,4,5-trimethoxystyryl)quinoxalin-2(1H)-one (6b). ^1H NMR (400 MHz, CDCl_3): δ 8.21 (d, $J = 16.1$ Hz, 1H), 7.92–7.87 (m, 1H), 7.67–7.54 (m, 4H), 7.36–7.27 (m, 4H), 6.90 (s, 2H), 6.67 (dd, $J = 7.8, 1.8$ Hz, 1H), 3.90 (s, 6H), 3.89 (s, 3H). ^{13}C NMR (126 MHz, CDCl_3): δ 154.92, 153.38, 152.89, 139.28, 139.01, 135.98, 133.62, 133.37, 132.14, 130.34, 129.49, 129.46, 129.40, 128.23, 124.16, 122.00, 115.49, 104.88, 61.01, 56.11; HRMS-ESI [M + H]⁺ m/z calcd for $\text{C}_{25}\text{H}_{23}\text{N}_2\text{O}_4$: 415.1652, found 415.1606.

2-((E)-2-(Benzo[d][1,3]dioxol-5-yl)vinyl)-3-phenoxyquinoxaline (5c). ^1H NMR (400 MHz, CDCl_3): δ 8.11 (d, $J = 15.9$ Hz, 1H), 8.05 (dd, $J = 7.8, 1.4$ Hz, 1H), 7.70 (dd, $J = 7.8, 1.5$ Hz, 1H), 7.64 (d, $J = 16.0$ Hz, 1H), 7.59 (td, $J = 7.3, 1.6$ Hz, 2H), 7.52 (t, $J = 7.9$ Hz, 2H), 7.36–7.31 (m, 3H), 7.29 (s, 1H), 7.20 (d, $J = 8.0$ Hz, 1H), 6.88 (d, $J = 8.0$ Hz, 1H), 6.03 (s, 2H). ^{13}C NMR (101 MHz, CDCl_3): δ 155.14, 153.04, 148.72, 148.33, 144.09, 139.91, 139.35, 137.29, 131.08, 129.62, 129.16, 128.41, 127.58, 127.29, 125.33, 123.73, 121.87, 119.02, 108.58, 106.40, 101.42; HRMS-ESI [M + H]⁺ m/z calcd for $\text{C}_{23}\text{H}_{17}\text{N}_2\text{O}_3$: 369.1234, found 369.1243.

(E)-3-(2-(Benzo[d][1,3]dioxol-5-yl)vinyl)-1-phenylquinoxalin-2(1H)-one (6c). ^1H NMR (400 MHz, CDCl_3): δ 8.19 (d, $J = 16.1$ Hz, 1H), 7.94–7.88 (m, 1H), 7.66 (t, $J = 7.4$ Hz, 2H), 7.59 (t, $J = 12.0$ Hz, 2H), 7.33 (t, $J = 7.1$ Hz, 3H), 7.26 (d, $J = 20.9$ Hz, 2H), 7.15 (d, $J = 8.1$ Hz, 1H), 6.85 (d, $J = 8.0$ Hz, 1H), 6.68 (d, $J = 7.7$ Hz, 1H), 6.03 (s, 2H). ^{13}C NMR (101 MHz, CDCl_3): δ 154.91, 153.17, 148.87, 148.29, 138.61, 136.07, 133.65, 133.39, 131.14,

130.34, 129.46, 129.36, 129.20, 128.27, 124.07, 124.05, 120.70, 115.42, 108.56, 106.44, 101.40; HRMS-ESI [M + H]⁺ m/z calcd for $\text{C}_{23}\text{H}_{17}\text{N}_2\text{O}_3$: 369.1234, found 369.1237.

(E)-2-Phenoxy-3-(4-(trifluoromethyl)styryl)quinoxaline (5d).

^1H NMR (400 MHz, CDCl_3): δ 8.10 (d, $J = 16.1$ Hz, 1H), 8.01–7.96 (m, 1H), 7.77 (dd, $J = 21.8, 12.1$ Hz, 3H), 7.63 (ddd, $J = 15.1, 8.5, 5.1$ Hz, 3H), 7.56–7.50 (m, 2H), 7.46–7.40 (m, 2H), 7.29–7.18 (m, 3H). ^{13}C NMR (126 MHz, CDCl_3): δ 155.26, 152.88, 143.17, 139.88, 139.83, 139.74, 135.70, 129.84, 129.68, 128.66, 127.83, 127.79, 127.37, 125.80, 125.77, 125.49, 123.38, 121.87; HRMS-ESI [M + H]⁺ m/z calcd for $\text{C}_{23}\text{H}_{16}\text{F}_3\text{N}_2\text{O}$: 393.1209, found 393.1225.

(E)-1-Phenyl-3-(4-(trifluoromethyl)styryl)quinoxalin-2(1H)-one (6d).

^1H NMR (500 MHz, CDCl_3): δ 8.17 (d, $J = 16.2$ Hz, 1H), 7.87–7.82 (m, 1H), 7.68 (dd, $J = 14.2, 12.3$ Hz, 3H), 7.56 (dd, $J = 10.1, 4.7$ Hz, 4H), 7.51 (d, $J = 7.5$ Hz, 1H), 7.28–7.21 (m, 4H), 6.62–6.57 (m, 1H). ^{13}C NMR (126 MHz, CDCl_3): δ 154.82, 152.55, 139.91, 136.95, 135.87, 133.88, 133.25, 130.42, 130.00, 129.74, 129.60, 128.21, 127.94, 125.79, 125.76, 124.99, 124.23, 115.55; HRMS-ESI [M + H]⁺ m/z calcd for $\text{C}_{23}\text{H}_{16}\text{F}_3\text{N}_2\text{O}$: 393.1209, found 393.1218.

(E)-2-(2-Chlorostyryl)-3-phenoxyquinoxaline (5e). ^1H NMR (500 MHz, CDCl_3): δ 8.02 (d, $J = 16.0$ Hz, 1H), 7.94 (dd, $J = 8.0, 1.8$ Hz, 1H), 7.67 (d, $J = 16.0$ Hz, 1H), 7.62–7.58 (m, 1H), 7.56 (d, $J = 8.6$ Hz, 2H), 7.51–7.48 (m, 2H), 7.40 (t, $J = 7.9$ Hz, 2H), 7.30 (d, $J = 8.5$ Hz, 2H), 7.22 (dd, $J = 5.9, 4.9$ Hz, 2H), 7.18–7.16 (m, 1H). ^{13}C NMR (126 MHz, CDCl_3): δ 154.15, 151.90, 142.55, 138.82, 138.53, 135.08, 133.96, 133.83, 128.59, 128.50, 128.03, 127.88, 127.51, 126.64, 126.30, 124.36, 120.80, 120.44, 28.68; HRMS-ESI [M + H]⁺ m/z calcd for $\text{C}_{22}\text{H}_{16}\text{ClN}_2\text{O}$: 359.0946, found 359.0951.

(E)-3-(2-Chlorostyryl)-1-phenylquinoxalin-2(1H)-one (6e). ^1H NMR (400 MHz, CDCl_3): δ 8.12 (d, $J = 16.2$ Hz, 1H), 7.87–7.81 (m, 1H), 7.65–7.49 (m, 5H), 7.27 (ddd, $J = 8.9, 7.2, 5.3$ Hz, 6H), 7.19 (s, 1H), 6.60 (dd, $J = 7.6, 2.0$ Hz, 1H). ^{13}C NMR (126 MHz, MeOD): δ 154.95, 152.42, 136.68, 136.01, 135.07, 134.79, 133.74, 133.23, 130.08, 129.70, 129.35, 129.07, 128.85, 128.76, 128.12, 124.12, 122.03, 115.36; HRMS-ESI [M + H]⁺ m/z calcd for $\text{C}_{22}\text{H}_{16}\text{ClN}_2\text{O}$: 359.0946, found 359.0952.

General procedure for the preparation of 2-phenoxyquinoxaline derivatives (8a–f) with aryne

To a stirred solution of 4, 6-diphenylpyridin-2(1H)-one (7a–f) (0.24 mmol, 1.0 equiv.) and trimethylsilyl phenyl triflate (2) (0.29 mmol, 1.2 equiv.) in acetonitrile as solvent, was added cesium fluoride (0.72 mmol, 3.0 equiv.) at room temperature. The mixture was stirred at room temperature for 4 h, after completing the reaction, reaction mixture was concentrated *in vacuo*. To the resulting residue, water was added, and the mixture was extracted with ethyl acetate three times. The combined organic phase was dried over sodium sulphate, and concentrated *in vacuo*. The crude product was purified by column chromatography (EtoAc in hexane), resulting the product.

2-Phenoxy-6-phenyl-4-(3,4,5-trimethoxyphenyl)pyridine (8a).

^1H NMR (400 MHz, CDCl_3): δ 7.87 (dd, $J = 8.0, 1.4$ Hz, 2H), 7.54



(d, $J = 1.1$ Hz, 1H), 7.36–7.27 (m, 5H), 7.17 (dd, $J = 8.6, 0.9$ Hz, 2H), 7.12 (dd, $J = 11.5, 4.2$ Hz, 1H), 6.89 (d, $J = 1.0$ Hz, 1H), 6.75 (s, 2H), 3.84 (s, 6H), 3.82 (s, 3H). ^{13}C NMR (126 MHz, CDCl_3): δ 163.92, 156.01, 154.38, 153.73, 153.26, 139.05, 138.49, 134.35, 129.54, 129.26, 128.70, 126.92, 124.45, 121.12, 113.54, 107.61, 104.44, 61.04, 56.36; HRMS-ESI $[\text{M} + \text{H}]^+$ m/z calcd for $\text{C}_{26}\text{H}_{24}\text{NO}_4$: 414.17, found 414.1687.

2-(4-Methoxyphenyl)-6-phenoxy-4-(3,4,5-trimethoxyphenyl)pyridine (8b). ^1H NMR (400 MHz, CDCl_3): δ 7.95 (d, $J = 8.9$ Hz, 2H), 7.59 (d, $J = 1.2$ Hz, 1H), 7.45 (dd, $J = 8.5, 7.4$ Hz, 2H), 7.28 (dd, $J = 8.6, 1.0$ Hz, 2H), 7.24 (dd, $J = 11.5, 4.2$ Hz, 1H), 6.95 (dd, $J = 9.0, 5.0$ Hz, 3H), 6.87 (s, 2H), 3.97 (s, 6H), 3.94 (s, 3H), 3.86 (s, 3H). ^{13}C NMR (101 MHz, CDCl_3): δ 163.83, 160.68, 155.73, 154.50, 153.72, 153.15, 139.14, 134.48, 131.13, 129.47, 128.23, 124.32, 121.09, 114.04, 112.63, 106.76, 104.57, 60.98, 56.37, 55.34; HRMS-ESI $[\text{M} + \text{H}]^+$ m/z calcd for $\text{C}_{27}\text{H}_{26}\text{NO}_5$: 444.1805, found 444.1799.

4-(3-Nitrophenyl)-2-phenoxy-6-phenylpyridine (8c). ^1H NMR (400 MHz, CDCl_3): δ 8.40 (t, $J = 1.9$ Hz, 1H), 8.19 (ddd, $J = 8.2, 2.2, 1.0$ Hz, 1H), 7.86 (ddd, $J = 4.6, 2.4, 1.4$ Hz, 3H), 7.56 (dd, $J = 11.3, 4.6$ Hz, 2H), 7.32 (ddd, $J = 8.1, 6.2, 4.6$ Hz, 5H), 7.19–7.11 (m, 3H), 6.91 (d, $J = 1.2$ Hz, 1H). ^{13}C NMR (126 MHz, CDCl_3): δ 164.20, 156.60, 154.08, 150.45, 148.79, 140.18, 137.99, 133.09, 130.21, 129.63, 129.56, 128.77, 126.93, 124.74, 123.82, 122.09, 121.27, 113.10, 107.50; HRMS-ESI $[\text{M} + \text{H}]^+$ m/z calcd for $\text{C}_{23}\text{H}_{17}\text{N}_2\text{O}_3$: 369.1234, found 369.1232.

4-(4-Bromophenyl)-2-(4-chlorophenyl)-6-phenoxyppyridine (8d). ^1H NMR (400 MHz, CDCl_3): δ 7.80 (d, $J = 8.7$ Hz, 2H), 7.51 (dd, $J = 12.8, 4.9$ Hz, 3H), 7.44–7.39 (m, 2H), 7.37–7.31 (m, 2H), 7.29 (d, $J = 8.7$ Hz, 2H), 7.18–7.12 (m, 3H), 6.87 (d, $J = 1.2$ Hz, 1H). ^{13}C NMR (126 MHz, CDCl_3): δ 164.18, 154.98, 154.12, 151.97, 137.17, 136.73, 135.40, 132.32, 129.64, 128.89, 128.68, 128.16, 124.71, 123.74, 121.24, 112.87, 107.39; HRMS-ESI $[\text{M} + \text{H}]^+$ m/z calcd for $\text{C}_{23}\text{H}_{16}\text{BrClNO}$: 436.0098, found 436.0095.

6-Phenoxy-4-phenyl-2,2'-bipyridine (8e). ^1H NMR (500 MHz, CDCl_3): δ 8.73–8.70 (m, 1H), 8.51 (d, $J = 1.3$ Hz, 1H), 8.25 (d, $J = 8.0$ Hz, 1H), 7.81–7.75 (m, 3H), 7.55–7.46 (m, 5H), 7.31 (dt, $J = 15.8, 4.2$ Hz, 4H), 7.16 (d, $J = 1.3$ Hz, 1H). ^{13}C NMR (126 MHz, CDCl_3): δ 163.89, 155.46, 154.69, 154.42, 153.27, 149.04, 138.14, 136.96, 129.62, 129.24, 129.02, 127.23, 124.53, 123.89, 121.45, 121.21, 114.18, 108.91; HRMS-ESI $[\text{M} + \text{H}]^+$ m/z calcd for $\text{C}_{22}\text{H}_{17}\text{N}_2\text{O}$: 325.1335, found 325.1337.

4-(Furan-2-yl)-2-phenoxy-6-phenylpyridine (8f). ^1H NMR (400 MHz, CDCl_3): δ 7.89 (dd, $J = 8.1, 1.5$ Hz, 2H), 7.66 (d, $J = 1.1$ Hz, 1H), 7.48–7.45 (m, 1H), 7.38–7.28 (m, 5H), 7.19–7.11 (m, 3H), 6.94 (d, $J = 1.1$ Hz, 1H), 6.81 (dd, $J = 3.4, 0.5$ Hz, 1H), 6.46 (dd, $J = 3.4, 1.8$ Hz, 1H). ^{13}C NMR (101 MHz, CDCl_3): δ 164.13, 156.25, 154.40, 151.49, 143.77, 141.75, 138.36, 129.56, 129.24, 128.64, 126.87, 124.46, 121.12, 112.10, 109.73, 108.95, 103.37; HRMS-ESI $[\text{M} + \text{H}]^+$ m/z calcd for $\text{C}_{21}\text{H}_{16}\text{NO}_2$: 314.1176, found 314.1118.

Conclusions

In conclusion, we have developed a simple, mild, metal free, efficient, room temperature method for the preparation of 4-phenoxy-2-phenylquinazoline, (E)-2-phenoxy-3-styrylquinoxaline and 2-phenoxyppyridine derivatives via an

aryne intermediate. The present method enables very easy preparation of phenoxylated quinazoline, quinaxazoline and pyridine derivatives that will be useful for a feasible access to the unnatural product molecules and their biological screening.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

MKZ thankful to the Council of Scientific and Industrial Research (CSIR) for the financial assistance. We are thankful to Deepika Singh for NMR spectral data analysis. One of the authors (Vivek) acknowledges the Department of Science & Technology for single crystal X-ray diffractometer as a National Facility under Project No. SR/S2/CMP-47/2003.

Notes and references

- (a) T. Kaicharla, M. Thangaraj and A. T. Biju, *Org. Lett.*, 2014, **16**, 1728; (b) C. Xie and Y. Zhang, *Org. Lett.*, 2007, **9**, 781; (c) H. Y. Li, L. J. Xing, M. M. Lou, H. Wang, R. H. Liu and B. Wang, *Org. Lett.*, 2015, **17**, 1098; (d) T. Truong, M. Mesgar, K. K. A. Le and O. Daugulis, *J. Am. Chem. Soc.*, 2014, **136**, 8568; (e) K. Neog, D. Dutta, B. Das and P. Gogoi, *Org. Lett.*, 2017, **19**, 730.
- (a) E. Yoshikawa and Y. Yamamoto, *Angew. Chem., Int. Ed.*, 2000, **39**, 173; (b) H. Yoshida, H. Fukushima, J. Ohshita and A. Kunai, *J. Am. Chem. Soc.*, 2006, **128**, 11040; (c) C. D. Gilmore, K. M. Allan and B. M. Stoltz, *J. Am. Chem. Soc.*, 2008, **130**, 1558.
- (a) K. M. Allan and B. M. Stoltz, *J. Am. Chem. Soc.*, 2008, **130**, 17270; (b) P. M. Tadross, S. C. Virgil and B. M. Stoltz, *Org. Lett.*, 2010, **12**, 1612; (c) U. K. Tambar, D. C. Ebner and B. M. Stoltz, *J. Am. Chem. Soc.*, 2006, **128**, 11752; (d) P. M. Tadross and B. M. Stoltz, *Chem. Rev.*, 2012, **112**, 3550.
- Y. Himeshima, T. Sonoda and H. Kobayashi, *Chem. Lett.*, 1983, **12**, 1211.
- A. Bhunia, S. R. Yetra and A. T. Biju, *Chem. Soc. Rev.*, 2012, **41**, 3140.
- H. Yoshida, E. Shirakawa, Y. Honda and T. Hiyama, *Angew. Chem., Int. Ed.*, 2002, **41**, 3247.
- (a) Y. L. Liu, Y. Liang, S. F. Pi and J. H. Li, *J. Org. Chem.*, 2009, **74**, 5691; (b) H. Yoshida, M. Watanabe, J. Ohshita and A. Kunai, *Tetrahedron Lett.*, 2005, **46**, 6729.
- S. S. Bhojgude, A. Bhunia, R. G. Gonnade and A. T. Biju, *Org. Lett.*, 2014, **16**, 676.
- (a) T. Roy and A. T. Biju, *Chem. Commun.*, 2018, **54**, 2580; (b) T. Matsuzawa, S. Yoshida and T. Hosoya, *Tetrahedron Lett.*, 2018, **59**, 4197; (c) M. Asamdi and K. H. Chikhalia, *Asian J. Org. Chem.*, 2017, **6**, 1331; (d) K. Okuma, *Heterocycles*, 2012, **85**, 515; (e) C. Wu and F. Shi, *Asian J. Org. Chem.*, 2013, **2**, 116; (f) A. G. Flores and R. Martin, *Synthesis*, 2013, **45**, 563; (g) P. M. Tadross and B. M. Stoltz, *Chem. Rev.*, 2012, **112**, 3550; (h) S. S. Bhojgude and A. T. Biju, *Angew. Chem., Int. Ed.*, 2012, **51**, 1520; (i) A. Bhunia, S. R. Yetra and A. T. Biju,



Chem. Soc. Rev., 2012, **41**, 3140; (j) C. M. Gampe and E. M. Carreira, *Angew. Chem., Int. Ed.*, 2012, **51**, 3766; (k) I. S. Kovalev, D. S. Kopchuk, G. V. Zyryanov, P. A. Slepukhin, V. L. Rusinov and N. O. Chupakhin, *Chem. Heterocycl. Compd.*, 2012, **48**, 536; (l) D. Perez, D. Pena and E. Guitian, *Eur. J. Org. Chem.*, 2013, 5981; (m) D. Wu, H. Ge, S. H. Liu and J. Yin, *RSC Adv.*, 2013, **3**, 22727; (n) J. Shi and Y. Li, *Chem. Soc. Rev.*, 2017, **46**, 1707.

10 D. G. Pintori and M. F. Greaney, *Org. Lett.*, 2009, **12**, 168.

11 J. C. Haber, M. A. Lynch, S. L. Spring, A. D. Pechulis, J. Raker and Y. Wang, *Tetrahedron Lett.*, 2011, **52**, 5847.

12 J. F. Wolfe, T. L. Rathman, M. C. Sleevi, J. A. Campbell and T. D. Greenwood, *J. Med. Chem.*, 1990, **33**, 161.

13 (a) P. P. Kung, M. D. Casper, K. L. Cook, L. Wilson-Lingardo, L. M. Risen, T. A. Vickers, R. Ranken, L. B. Blyn, J. R. Wyatt and P. D. Cook, *J. Med. Chem.*, 1999, **42**, 4705; (b) L. S. Reddy and B. E. Naik, *Heterocycl. Lett.*, 2019, **9**(4), 487.

14 M. Saeedi, M. Mohammadi-Khanaposhtani, P. Pourrabia, N. Razzaghi, R. Ghadimi, S. Imanparast, M. A. Faramarzi, F. Bandarian, E. N. Esfahani, M. Safavi, M. Safavi, H. Rastegar, B. Larijani, M. Mahdavi and T. Akbarzadeh, *Bioorg. Chem.*, 2019, **83**, 161.

15 X.-W. Wei, J.-M. Yuan, W.-Y. Huang, N.-Y. Chen, X.-J. Li, C.-X. Pan, D.-L. Mo and G.-F. Su, *Eur. J. Med. Chem.*, 2020, **186**, 111851.

16 (a) Y. B. Kim, Y. H. Kim, J. Y. Park and S. K. Kim, *Bioorg. Med. Chem. Lett.*, 2004, **14**, 541; (b) J. Peng, D. Kong, L. Liu, S. Song, H. Kuang and C. Xu, *Anal. Methods*, 2015, **7**, 5204.

17 (a) E. Moreno, S. Ancizu, S. P. Silanes, E. Torres, I. Aldana and A. Monge, *Eur. J. Med. Chem.*, 2010, **45**, 4418; (b) L. E. Seitz, W. J. Suling and R. C. Reynolds, *J. Med. Chem.*, 2002, **45**, 5604.

18 (a) E. Tombary and E. Hawash, *Med. Chem.*, 2014, **10**, 521; (b) M. A. Henen, S. E. Bialy, F. E. Goda, M. N. A. Nasr and H. M. Eisa, *Med. Chem. Res.*, 2012, **21**, 2368; (c) L. M. Wilhelmsson, N. Kingi and J. Bergman, *J. Med. Chem.*, 2008, **51**, 7744.

19 Y.-C. Zhang, Q. Shen, M.-W. Zhu, J. Wang, Y. Du, J. Wu and J.-X. Li, *ChemistrySelect*, 2020, **5**(4), 1526.

20 (a) A. A. Elhelby, R. R. Ayyad and M. F. Zayed, *Arzneim. Forsch.*, 2011, **61**, 379; (b) E. Elkaeed, A. Ghiaty, A. E. Morsy, K. E. Gamal and H. Sakr, *Chem. Sci. Rev. Lett.*, 2014, **3**, 1375.

21 L. J. Farrugia, *J. Appl. Crystallogr.*, 1997, **30**, 565.

22 L. J. Farrugia, *J. Appl. Crystallogr.*, 1999, **32**, 837.

23 M. Nardelli, *J. Appl. Crystallogr.*, 1995, **28**, 659.

24 A. L. Spek, *Acta Crystallogr., Sect. D: Biol. Crystallogr.*, 2009, **65**, 148–155.

25 G. M. Sheldrick, *Acta Crystallogr., Sect. A: Found. Crystallogr.*, 2008, **64**, 112.

