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Convenient synthesis of benzo[*b*]pyrazolo[5,1-*f*][1,6]naphthyridines by silver triflate catalyzed three-component reaction of 2-alkynyl-3-formylquinolines, tosylhydrazine and carbonyl compounds

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ABSTRACT

Benzo[*b*]pyrazolo[5,1-*f*][1,6]naphthyridines were prepared by silver triflate catalyzed one-pot cyclization of tosylhydrazine, carbonyl compounds and 2-alkynyl-3-formylquinolines, which are available by Sonogashira reaction of 2-chloro-3-formylquinoline.

1. Introduction

Quinolines, isoquinolines, naphthyridines and their polycyclic derivatives are found in many natural products and biologically active molecules (Fig. 1).[1–6] 1,6-Naphthyridines exhibit a broad range of pharmacological activities, including antifungal, antimalarial, antihypertensive, antitumour and antihistaminic activity.[2–5] The lamellarin alkaloids, which constitute a family of novel marine natural products, contain a highly substituted fused 1,2-dihydroisoquinoline core.[5] Lamellarin D has been discovered as a potent inhibitor of human topoisomerase-1,[5] and lamellarin α-20-sulfate displays selective inhibition against HIV-1 integrase in vitro.[3,7] Wu and co-workers found that pyrazolo[5,1-*a*]isoquinolines are inhibitors of PTP1B (protein tyrosine phosphatase 1 B, IC_{50} 1.75 μg/mL).[8] 1,6-Naphthyridines exhibit anti-HSV activity as well as inhibition of HIV-1 integrase, HCMV, FGF receptor-1 tyrosine kinase and of acetylcholinesterase (Fig. 1).[8] Herpes simplex virus type-1 (HSV-1) is the primary cause of facial lesions (mouth, lips and eyes) in humans. The widespread use of acyclovir and nucleoside analogues has led to the increase of HSV strains, which are resistant to these drugs.

Kolodziejczyk and Orito reported a new synthesis of pyrazolonaphthyridines by multi-component reactions.[9] Denny and co-workers prepared 3-aryl-7-halo-1,6-naphthyridin-2-amines and 3-aryl-7-halo-1,6-naphthyridin-2(1*H*)-ones by diazotization of 3-aryl-1,6-naphthyridine-2,7-diamines.[10] Recently, Wu and co-workers reported the synthesis of pyrazolo[5,1-*a*]isoquinolines by silver triflate catalyzed multi-component reaction of 2-alkynylbenzaldehydes, tosylhydrazine and ketones or aldehydes.[11] Herein, we report the first application of this methodology to a heterocyclic substrate. The one-pot reaction of readily available 2-alkynyl-3-formylquinolines with tosylhydrazine, and ketones or aldehydes provides a new and convenient approach to benzo[*b*]pyrazolo[5,1-*f*][1,6]naphthyridines, which are not readily available by other methods.

2. Results and discussion

2-Chloroquinoline-3-carbaldehyde (**2**) was prepared, following a known procedure,[12] by Vilsmeier reaction of acetanilide (**1**). The-Sonogashira coupling of **2** with various alkynes afforded the

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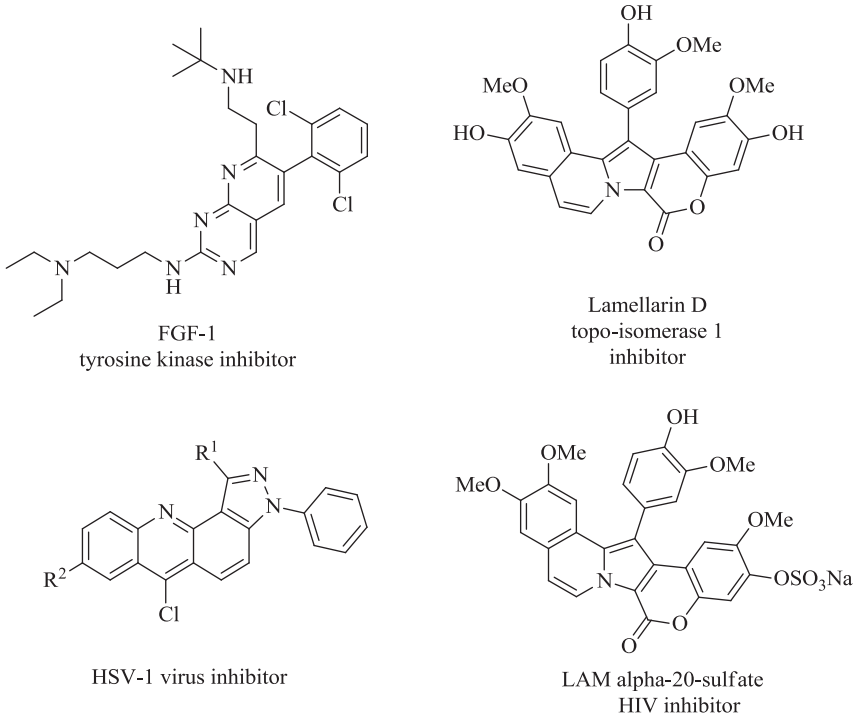
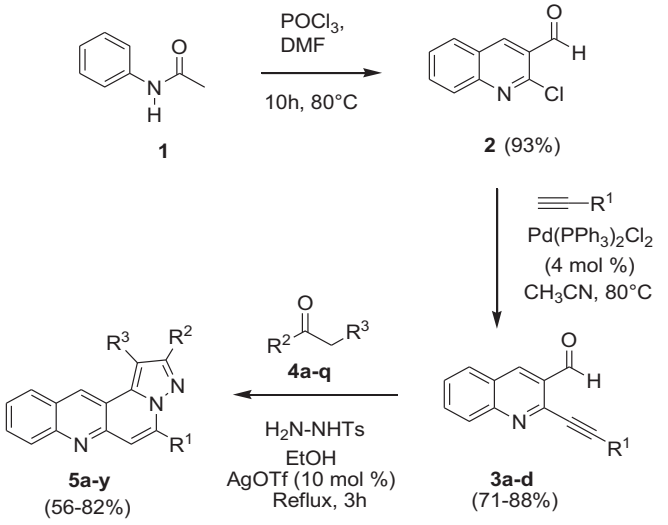


Fig. 1. Polycyclic quinolines, isoquinolines and naphthyridines as clinically used drugs.

known[13] 2-alkynyl-3-formylquinolines **3a**–**d** (Scheme 1, Table 1). The cyclization of **3a**–**d** with tosylhydrazine and various carbonyl compounds (**4**), in the presence of silver triflate (AgOTf)[14,15] (10 mol %) and a base, afforded the benzo[*b*]pyrazolo[5,1-*f*][1,6] naphthyridines **5a**–**y** in 56–82% yields (Table 2). The best yields were obtained when K_3PO_4 (3.0 equiv) and EtOH were used as base and solvent, respectively, and when the reactions were carried out under reflux. The reaction in the absence of AgOTf or the employment of other Lewis acids resulted in a decrease of the yield (Table 3).



Scheme 1. Synthesis of benzo[*b*]pyrazolo[5,1-*f*][1,6]naphthyridines **5a**–**y**.

Both aryl and alkyl substituted alkynes could be successfully employed to give products **5a**–**o** and **5p**–**x**, respectively. The unsubstituted product **5y** (R^1=H) was prepared from TMS substituted derivative **3d**. The use of (aromatic and aliphatic)

Table 1
Synthesis of 2-alkynyl-3-formylquinolines **3a**–**d**

3	R^1	3 (%)[a]
a	Ph	88
b	Pent	84
c	^{c}Pr	74
d	$SiMe_3$	71

[a] Yields of isolated products.

Table 2
Synthesis of benzo[*b*]pyrazolo[5,1-*f*][1,6]naphthyridines **5a**–**y**

3	4	5	R^1	R^2	R^3	5 (%)[a]
a	**a**	**a**	C_6H_5	H	*n*-C_3H_7	82
a	**b**	**b**	C_6H_5	H	*n*-C_6H_{13}	75
a	**c**	**c**	C_6H_5	H	*n*-C_8H_{17}	68
a	**d**	**d**	C_6H_5	H	*n*-$C_{10}H_{21}$	70
a	**e**	**e**	C_6H_5	H	H_2C=$CH(CH_2)_6$	60
a	**f**	**f**	C_6H_5	CH_3	H	91
a	**g**	**g**	C_6H_5	C_2H_5	CH_3	84
a	**h**	**h**	C_6H_5		$-(CH_2)_3-$	64
a	**i**	**i**	C_6H_5		$-(CH_2)_4-$	87
a	**j**	**j**	C_6H_5		$CH(CH_3)-(CH_2)_3-$	75
a	**k**	**k**	C_6H_5		$-(CH_2)_5-$	63
a	**l**	**l**	C_6H_5		$-(CH_2)_6-$	60
a	**m**	**m**	C_6H_5	CH_3	CO_2CH_3	84
a	**n**	**n**	C_6H_5	C_6H_5	C_2H_5	64
a	**o**	**o**	C_6H_5	H	4-(MeO)C_6H_4	62
b	**p**	**p**	*n*-C_5H_{11}	CH_3	H	72
b	**a**	**q**	*n*-C_5H_{11}	H	*n*-C_3H_7	72
b	**i**	**r**	*n*-C_5H_{11}		$-(CH_2)_4-$	66
b	**q**	**s**	*n*-C_5H_{11}		$-(CH_2)_2-CH(CH_3)-CH_2-$	75
b	**h**	**t**	*n*-C_5H_{11}		$-(CH_2)_3-$	76
b	**g**	**u**	*n*-C_5H_{11}	C_2H_5	C_2H_5	89
c	**j**	**v**	^{c}Pr		$CH(CH_3)-(CH_2)_3-$	75
c	**a**	**w**	^{c}Pr	H	*n*-C_3H_7	74
c	**i**	**x**	^{c}Pr		$-(CH_2)_4-$	76
d	**a**	**y**	H[b]	H	*n*-C_3H_7	72

[a] Yields of isolated products.
[b] Prepared from **3d** (R^1=$SiMe_3$).

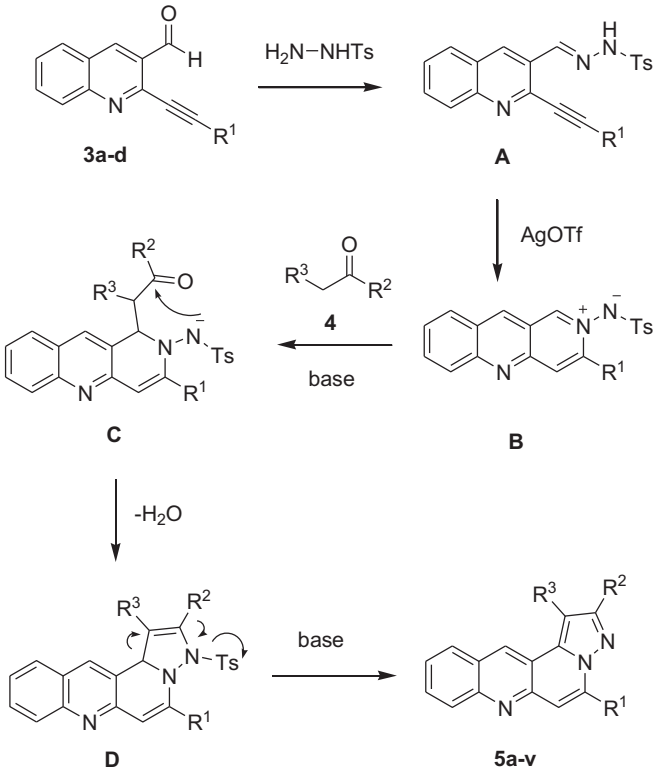
Table 3
Optimization of the reaction conditions for **5a**

Entry	Catalyst	Solvent	Base	T (°C)	Time (h)	**5a** (%)[a]
1	AgOTf	EtOH	K_3PO_4	70	6	82
2	AgOTf	EtOH	K_2CO_3	70	6	73
3	AgOTf	EtOH	DIPA	70	6	27
4	AgOTf	EtOH	Proline	70	7	36
5	AgOTf	EtOH	Piperidine	70	6	28
6	AgOTf	EtOH	TEA	70	6	37
7	—	EtOH	K_3PO_4	70	7	15
8	AgOTf	MeCN	K_3PO_4	90	7	55
9	$Pd(PPh_3)_2Cl_2$	Toluene	K_3PO_4	90	3	67
10	$Pd(PPh_3)_4$	Toluene	K_3PO_4	90	9	47
11	AgOTf	Toluene	K_3PO_4	90	9	34

[a] Yields of isolated products.

aldehydes and ketones was equally successful. The use of cyclic ketones resulted in the formation of the corresponding pentacyclic products **5h**–**l**, **5r**–**t**, **5v** and **5x**. Most of the ketones were either symmetrical, such as acetone (**4f**), pentan-3-one (**4g**), cyclohexanone (**4i**) or 4-methylcyclohexanone (**4q**) or they contain only one enolizable carbon atom adjacent to the carbonyl group, such as propiophenone (**5n**). Therefore, no issue of regioselectivity had to be considered in these reactions. The cyclization of **3a** with (unsymmetrical) methyl acetoacetate (**4m**), product **5m** was formed with very good regioselectivity. The selectivity can be explained by the higher acidity of the central CH_2 group as compared to the terminal CH_3 group of **4m**. In case of (unsymmetrical) 2-methylcyclohexanone (**4j**) the cyclizations proceeded regioselectively via the sterically less hindered carbon atom C-6 to give products **5j** and **5v**.

The formation of the products can be explained in analogy to the mechanism suggested by Wu and co-workers:[11] The reaction of **3a**–**d** with tosylhydrazine afforded hydrazone **A** (Scheme 2). The Lewis acid catalyzed attack of the nitrogen atom to the triple bond gave zwitterionic intermediate **B**. The reaction of the iminium ion



Scheme 2. Possible mechanism of the formation of **5a**–**v**.

with the carbonyl compound provided intermediate **C**, which underwent a cyclization by attack of the nitrogen atom to the carbonyl group to give **D**. Base mediated cleavage of the tosyl group resulted in aromatization and formation of **5a**–**v**.

In conclusion, we have reported an efficient synthesis of benzo[*b*]pyrazolo[5,1-*f*][1,6]naphthyridines by AgOTf-catalyzed one-pot cyclization of 2-alkynyl-3-formylquinolines, tosylhydrazine and carbonyl compounds.

3. Experimental section

3.1. General

Reactions were carried out under inert atmosphere (Argon 4.6) in order to simultaneously exclude oxygen and water when appropriate. Pressure tubes were used to avoid condenser. Solvents for reactions were dried and distilled by standard methods or purchased from Merck®, Aldrich®, Acros Organics® and others whenever exclusion of water was desired. Solvents for liquid chromatography and extraction were always distilled prior to use and partly reused after fractional distillation (*n*-heptane, ethyl acetate). NMR Spectroscopy: Bruker AC 250, Bruker ARX 300, Bruker ARX 500. For NMR characterization the one-dimensional ^{1}H NMR, proton-decoupled ^{13}C NMR and DEPT 135 spectra were collected. If necessary other techniques (NOESY, COSY, HMQC and HMBC) were applied as well. All NMR spectra presented in this work, were collected in DMSO-d_6 and $CDCl_3$solution. All chemical shifts were given in parts per million. References (^{1}H NMR): TMS (δ=0.00) or residual $CHCl_3$ (δ=7.26) were taken as internal standard. References (^{13}C NMR): TMS (δ=0.0) or residual $CHCl_3$ (δ=77.0) were taken as internal standard. Multiplicities are given as follows: s=singlet, d=doublet, t=triplet, q=quartet, m=multiplet, br=broad signal. More complex coupling patterns are represented by combinations of the respective symbols. For example, td indicates a triplet of doublets with the larger coupling constant associated with the first symbol (here: triplet). Infrared Spectroscopy (IR): Nicolet 205 FT-IR, Nicolet Protége 460 FT-IR Peaks are given the following assignments: w=weak, m=medium, s=strong, br=broad. Mass Spektrometry (MS): AMD MS40, Varian MAT CH 7, MAT 731 (EI, 70 eV), Intecta AMD 402 (EI, 70 eV and CI), Finnigan MAT 95 (CI, 200 eV). High Resolution Mass Spectrometry (HRMS): Varian MAT 311, Intecta AMD 402. Elemental Analysis: LECO CHNS-932 Thermoquest Flash EA 1112. Melting Points: Micro heating table HMK 67/1825 Kuestner (Büchi Apparatus). Leitz Labolux 12 Pol with heating table Mettler FP 90. Melting points are uncorrected. X-ray crystal structure analysis: Bruker X8Apex Diffractometer with CCD-Kamera (Mo Kα und Graphit Monochromator, λ=0.71073 Å) or Bruker Apex Kappa-II CCD diffractometer using graphite monochromated Mo Kα radiation (λ=0.71073). Thin Layer Chromatography (TLC): Merck Kiesel gel 60 F_{254} on aluminium foil from Macherey–Nagel. Detection was carried out under UV light at 254 nm and 365 nm. As colourizing reagent the following mixtures were used: 1–2/100 *p*-anisaldehyde or vanillin, 10/100 glacial acetic acid, 5/100 sulfuric acid, 83–84/100 methanol. *Column chromatography*: Column chromatography was performed with Merck Silica Gel 60 or Macherey–Nagel Silica Gel 60 (0.063–0.200 mm, 70–230 mesh). The finer Merck Silica Gel 60 (0.040–0.063 mm, 230–400 mesh) was chosen when appropriate.

3.2. Synthesis of 2-alkynylquinoline-3-carbaldehydes 3a–d

The known products **3a**–**d** were prepared by the following reported procedure:[13] the reaction of **2** (0.25 mmol) with alkynes (0.26 mmol) were carried out in the presence of $Pd(PPh_3)_2Cl_2$ (4 mol %), triphenylphosphine (8 mol %) and triethylamine (2 equiv) in CH_3CN as a solvent at 80 °C under an inert atmosphere for 3–6 h (TLC control). The reaction mixture was concentrated in vacuo and

the residue was purified by column chromatography on silica gel using EtOAc/hexane as eluent.

3.3. Synthesis of benzo[*b*]pyrazolo[5,1-*f*][1,6]naphthyridines 5a–v

2-Alkynylquinoline-3-carbaldehyde **3** (0.3 mmol) was added to a solution of tosylhydrazine (0.3 mmol) in EtOH (3 ml). The mixture was stirred at room temperature for 10 min. Then AgOTf (7.7 mg, 10 mol %) was added and the reaction mixture was heated to 70 °C. Subsequently, **4** (0.6 mmol) and K_3PO_4 (0.9 mmol) were added to the mixture. After completion of reaction as indicated by TLC, the mixture was diluted with ethyl acetate (5.0 ml) and quenched with H_2O (5.0 ml). The organic layer was washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. The residue obtained was purified by flash chromatography column on silica gel to provide the desired product **5**.

*3.3.1. 5-Phenyl-1-propylbenzo[b]pyrazolo[5,1-f][1,6]naphthyridine (**5a**).* Starting with 2-(phenylethynyl)quinoline-3-carbaldehyde **3a** (150 mg, 0.58 mmol), sulfonohydrazide (186 mg, 1.0 mmol), pentanal **4a** (0.083 mg, 0.96 mmol), AgOTf (10 mol %), K_3PO_4 (1.8 mmol) in EtOH (3 ml), **5a** was isolated after column chromatography (silica gel, *n*-heptane/EtOAc=9:1) as a yellowish solid (107 mg, 82%), mp=150–152 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ=1.09 (t, *J*=7.3 Hz, 3H, CH_3), 1.80–1.92 (m, 2H, CH_2), 3.04 (t, *J*=7.8 Hz, 2H, CH_2), 7.25 (s, 1H, Ar), 7.44–7.55 (m, 4H, Ar), 7.67–7.74 (m, 1H, Ar), 7.82–7.87 (m, 3H, Ar), 7.93 (d, *J*=8.6 Hz, 1H, Ar), 8.10 (d, *J*=8.6 Hz, 1H, Ar), 8.81 (s, 1H, Ar). ^{13}C NMR (75 MHz, $CDCl_3$): δ=14.2 (CH_3), 22.2, 28.2 (CH_2), 113.2 (CH), 119.0, 119.74 (C), 126.4 (CH), 126.5, 147.8 (C), 128.2, 128.4, 128.4, 128.8, 129.5, 129.5, 129.8, 130.2, 130.4 (CH), 133.3, 133.4 (C), 141.7 (CH), 143.6, 147.7 (C). IR (ATR): $\tilde{\nu}$=1614, 1492 (w), 1460, 1334 (m), 1049 (w), 912 (m), 744 (s), 617 (m) cm^{-1}. GC–MS (EI, 70 eV): *m*/*z* (%)=337 (39, M^+), 309 (24), 308 (100), 154 (16). HRMS (EI): calcd for $C_{23}H_{19}N_3$ $[M]^+$: 337.1573. Found: 337.1573.

*3.3.2. 1-Hexyl-5-phenylbenzo[b]pyrazolo[5,1-f][1,6]naphthyridine (**5b**).* Starting with 2-(phenylethynyl)quinoline-3-carbaldehyde **3a** (150 mg, 0.58 mmol), sulfonohydrazide (186 mg, 1.0 mmol), octanal **4b** (123 mg, 0.96 mmol), AgOTf (10 mol %), K_3PO_4 (1.8 mmol) in EtOH (3 ml), **5b** was isolated after column chromatography (silica gel, *n*-heptane/EtOAc=9:1) as a yellowish solid (110 mg, 75%), mp=103–105 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ=0.87 (t, *J*=6.8 Hz, 3H, CH_3), 1.34–1.36 (m, 4H, CH_2), 1.5 (p, *J*=7.0 Hz, 2H, CH_2), 1.82 (p, *J*=7.0 Hz, 2H, CH_2), 3.04 (t, *J*=7.3 Hz, 2H, CH_2), 7.49–7.51 (m, 4H, Ar), 7.24 (s, 1H, Ar), 7.83–7.86 (m, 3H, Ar), 7.70–7.73 (m, 1H, Ar), 7.92 (d, *J*=8.1 Hz, 1H, Ar), 8.10 (d, *J*=8.2 Hz, 1H, Ar), 8.79 (s, 1H, Ar). ^{13}C NMR (75 MHz, $CDCl_3$): δ=14.1 (CH_3), 22.7 (CH_2), 26.1, 28.89, 29.4, 31.8 (CH_2), 113.3 (CH), 119.3, 119.7 (C), 126.4 (CH), 126.5 (C), 128.1, 128.4, 128.4, 128.9, 129.5, 129.8, 129.8, 130.1, 130.3 (CH), 133.3, 133.4 (C), 141.6 (CH), 143.6, 147.7, 147.8 (C). IR (ATR): $\tilde{\nu}$=1613, 1492 (w), 1456 (m), 1170, 1073 (w), 910 (m), 740, 694 (s), 618 (m) cm^{-1}. GC–MS (EI, 70 eV): *m*/*z* (%)=379 (33, M^+), 309 (24), 308 (100), 154 (6). HRMS (EI): calcd for $C_{26}H_{25}N_3$ $[M]^+$: 379.2043. Found: 379.2043.

*3.3.3. 1-Octyl-5-phenylbenzo[b]pyrazolo[5,1-f][1,6]naphthyridine (**5c**).* Starting with 2-(phenylethynyl)quinoline-3-carbaldehyde (**3a**) (150 mg, 0.58 mmol), sulfonohydrazide (186 mg, 1 mmol), decanal (**4c**) (150 mg, 0.96 mmol), AgOTf (10 mol %), K_3PO_4 (1.8 mmol) in EtOH (3 ml), **5c** was isolated after column chromatography (silica gel, *n*-heptane/EtOAc=9:1) as a yellowish solid (100 mg, 68%), mp=70–72 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ=0.78–0.81 (m, 3H, CH_3), 1.17–1.19 (m, 10H, CH_2), 1.78 (p, *J*=8.3 Hz, 2H, CH_2), 3.01 (t, *J*=7.7 Hz, 2H, CH_2), 7.2 (s, 1H, Ar), 7.43–7.45 (m, 4H, Ar), 7.65–7.67 (m, 1H, Ar), 7.81–7.83 (m, 4H, Ar), 8.03 (d, *J*=8.3 Hz, 1H, Ar), 8.73 (s, 1H, Ar). ^{13}C NMR (75 MHz, $CDCl_3$): δ=14.1 (CH_3), 22.7, 26.1, 28.9, 29.4, 29.5, 29.7, 31.9 (CH_2), 118.3 (CH), 119.2, 119.7 (C), 126.3, 126.5, 128.1, 128.4, 28.4, 128.9, 129.5, 129.5, 129.7, 130.0, 130.3, 133.3 (CH), 133.4 (C), 141.6 (CH), 143.5, 147.7, 147.9 (C). IR (ATR): $\tilde{\nu}$=1614, 1493 (w), 1459, 1338 (s), 1226, 989 (w), 911, 857, 694 (m) cm^{-1}. GC–MS (EI, 70 eV): *m*/*z* (%)=407 (37, M^+), 309 (27), 308 (100), 154 (6). HRMS (EI): calcd for $C_{28}H_{29}N_3$ $[M]^+$: 407.2356. Found: 407.2357.

*3.3.4. 1-Decyl-5-phenylbenzo[b]pyrazolo[5,1-f][1,6]naphthyridine (**5d**).* Starting with 2-(phenylethynyl)quinoline-3-carbaldehyde (**3a**) (150 mg, 0.58 mmol), sulfonohydrazide (186 mg, 1 mmol), dodecanal (**4d**) (177 mg, 0.96 mmol), AgOTf (10 mol %), K_3PO_4 (1.8 mmol) in EtOH (3 ml), **5d** was isolated after column chromatography (silica gel, *n*-heptane/EtOAc=9:1) as a yellowish solid (112 mg, 70%), mp=56–58 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ=0.81 (t, *J*=6.6 Hz, 3H, CH_3), 1.20–1.21 (m, 12H, CH_2), 1.47–1.49 (m, 2H, CH_2), 1.80 (p, *J*=8.1 Hz, 2H, CH_2), 3.03 (t, *J*=7.6 Hz, 2H, CH_2), 7.23 (s, 1H, Ar), 7.46–7.47 (m, 4H, Ar), 7.68–7.69 (m, 1H, Ar), 7.82–7.83 (m, 3H, Ar), 7.91 (d, *J*=8.1 Hz, 1H, Ar), 8.11 (d, *J*=8.5 Hz, 1H, Ar), 8.79 (s, 1H, Ar). ^{13}C NMR (75 MHz, $CDCl_3$): δ=14.1 (CH_3), 22.7, 26.1, 28.9, 29.4, 29.5, 29.6, 29.7, 29.7, 31.9 (CH_2), 113.4 (CH), 119.3, 119.7 (C), 126.4, 126.5, 128.2, 128.4, 128.4, 128.9, 129.6, 129.6, 129.8, 130.1, 130.3 (CH), 133.3, 133.4 (C), 141.7 (CH), 143.5, 147.8, 147.9 (C). IR (ATR): $\tilde{\nu}$=2915 (s), 1614, 1492 (w), 1456 (s), 1340 (m), 1072 (w), 912, 852 (m), 743, 687 (s), 619 (m) cm^{-1}. GC–MS (EI, 70 eV): *m*/*z* (%)=379 (33, M^+), 309 (24), 308 (100), 154 (6). HRMS (EI): calcd for $C_{30}H_{33}N_3$ $[M]^+$: 435.2669. Found: 435.2666.

*3.3.5. 1-(Non-8-en-1-yl)-5-phenylbenzo[b]pyrazolo[5,1-f][1,6]naphthyridine (**5e**).* Starting with 2-(phenylethynyl)quinoline-3-carbaldehyde (**3a**) (150 mg, 0.58 mmol), sulfonohydrazide (186 mg, 1 mmol), undecylenic aldehyde (**4e**) (161 mg, 0.96 mmol), AgOTf (10 mol %), K_3PO_4 (1.8 mmol) in EtOH (3 ml), **5e** was isolated after column chromatography (silica gel, *n*-heptane/EtOAc=9:1) as a yellowish solid (97 mg, 60%), mp=77–79 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ=1.33–1.35 (m, 8H, CH_2), 1.80–1.81 (m, 2H, CH_2), 1.96–1.98 (m, 2H, CH_2), 3.02 (t, *J*=7.7 Hz, 2H, CH_2), 5.71–5.73 (m, 1H, Ar), 4.86–4.88 (m, 2H, C=C), 7.22 (s, 1H, Ar), 7.47–7.49 (m, 4H, Ar), 7.67–7.68 (m, 1H, Ar), 7.81 (s, 1H, Ar), 7.83–7.85 (m, 2H, Ar), 7.90 (d, *J*=8.5 Hz, 1H, Ar), 8.07 (d, *J*=8.5 Hz, 1H, Ar), 8.77 (s, 1H, Ar). ^{13}C NMR (75 MHz, $CDCl_3$): δ=26.1, 28.9, 28.9, 29.1, 29.4, 29.6, 33.8 (CH_2), 113.4 (CH), 114.3 (CH_2), 119.2, 119.7 (C), 126.4 (CH), 126.5 (C), 128.1, 128.4, 128.4, 128.9, 129.5, 129.8 (CH), 129.8, 130.0, 130.3 (CH), 133.3, 133.4 (C), 139.1, 141.1 (CH), 143.49, 147.8, 147.9 (C). IR (ATR): $\tilde{\nu}$=2920 (m), 1613, 1492 (w), 1457 (m), 1358 (w), 1336 (m), 1138, 988 (w), 896, 745, 692 (s), 618 (m) cm^{-1}. GC–MS (EI, 70 eV): *m*/*z* (%)=420 (11, M^++1), 419 (34, M^+), 309 (27), 308 (100). HRMS (EI): calcd for $C_{29}H_{29}N_3$ $[M]^+$: 419.2356. Found: 419.2354.

*3.3.6. 2-Methyl-5-phenylbenzo[b]pyrazolo[5,1-f][1,6]naphthyridine (**5f**).* Starting with 2-(phenylethynyl)quinoline-3-carbaldehyde (**3a**) (150 mg, 0.58 mmol), sulfonohydrazide (186 mg, 1 mmol), acetone (**4f**) (0.057 mg, 0.96 mmol), AgOTf (10 mol %), K_3PO_4 (1.8 mmol) in EtOH (3 ml), **5f** was isolated after column chromatography (silica gel, *n*-heptane/EtOAc=9:1) as a yellowish solid (107 mg, 91%), mp=150–152 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ=2.41 (s, 3H, CH_3), 6.88 (s, 1H, Ar), 7.16 (s, 1H, Ar), 7.43–7.45 (m, 4H, Ar), 7.63–7.66 (m, 1H, Ar), 7.81 (d, *J*=8.1 Hz, 1H, Ar), 7.84–7.87 (m, 2H, Ar), 8.03 (d, *J*=8.2 Hz, 1H, Ar), 8.59 (s, 1H, Ar). ^{13}C NMR (75 MHz, $CDCl_3$): δ=14.3 (CH_3), 100.7 (CH), 122.9 (C), 125.4 (CH), 125.5 (C), 126.3 (CH), 127.1 (C), 127.9, 128.4, 128.4, 128.6, 129.5, 129.8, 130.2, 130.3, 133.3 (CH), 139.2, 143.1, 147.3, 148.7, 148.9, 151.1 (C). IR (ATR): $\tilde{\nu}$=1613, 1555, 1494 (w), 1428, 1328 (m), 1180, 858 (w), 793 (m), 747, 693 (s), 622 (m) cm^{-1}. GC–MS (EI, 70 eV): *m*/*z* (%)=310 (18, M^++1), 309 (89, M^+), 308 (100), HRMS (EI): calcd for $C_{21}H_{15}N_3$ $[M]^+$: 309.1250. Found: 309.1250.

*3.3.7. 1-Ethyl-2-methyl-5-phenylbenzo[b]pyrazolo[5,1-f][1,6]naphthyridine (**5g**).* Starting with 2-(phenylethynyl)quinoline-3-

carbaldehyde (**3a**) (150 mg, 0.58 mmol), sulfonohydrazide (186 mg, 1 mmol), 2-pentanon (**4g**) (0.081 mg, 0.96 mmol), AgOTf (10 mol %), K_3PO_4 (1.8 mmol) in EtOH (3 ml), **5g** was isolated after column chromatography (silica gel, *n*-heptane/EtOAc=9:1) as a yellowish solid (111 mg, 84%), mp=189–191 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ=1.24 (t, *J*=7.1 Hz, 3H, CH_3), 2.54 (s, 3H, CH_3), 2.76 (q, *J*=6.3 Hz, 2H, CH_2), 7.13 (s, 1H, Ar), 7.42–7.44 (m, 4H, Ar), 7.64 (t, *J*=7.1 Hz, 1H, Ar), 7.84 (d, *J*=8.7 Hz, 1H, Ar), 7.90–7.92 (m, 2H, Ar), 8.03 (d, *J*=8.5 Hz, 1H, Ar), 8.74 (s, 1H, Ar). ^{13}C NMR (75 MHz, $CDCl_3$): δ=10.7, 13.9 (CH_3), 20.0 (CH_2), 111.1 (C), 112.2 (CH), 119.8 (C), 126.1 (CH), 126.4 (C), 128.1, 128.2, 128.6, 128.6, 128.8, 129.6, 129.6, 129.7, 130.1 (CH), 133.5, 134.5, 143.3, 147.8, 148.1, 155.5 (C). IR (ATR): $\tilde{\nu}$=1613, 1555, 1494 (w), 1428, 1328 (m), 1180, 858 (w), 793 (m), 747, 693 (s), 622 (m) cm^{-1}. GC–MS (EI, 70 eV): *m*/*z* (%)=338 (24, M^++1), 337 (100, M^+), 336 (54), 281 (22). HRMS (EI): calcd for $C_{23}H_{19}N_3$ $[M]^+$: 337.1573. Found: 337.1571.

*3.3.8. 6-Phenyl-2,3-dihydro-1H-benzo[b]cyclopenta[3,4]pyrazolo [5,1-f][1,6]naphthyridine (**5h**).* Starting with 2-(phenylethynyl) quinoline-3-carbaldehyde (**3a**) (150 mg, 0.58 mmol), sulfonohydrazide (186 mg, 1 mmol), cyclopentanone (**4h**) (0.081 mg, 0.96 mmol), AgOTf (10 mol %), K_3PO_4 (1.8 mmol) in EtOH (3 ml), **5h** was isolated after column chromatography (silica gel, *n*-heptane/EtOAc=9:1) as a yellowish solid (83 mg, 64%), mp=223–225 °C. ^{1}H NMR (250 MHz, $CDCl_3$): δ=2.56 (q, *J*=7.6 Hz, 2H, CH_2), 2.87 (t, *J*=6.7 Hz, 2H, CH_2), 3.01 (t, *J*=6.7 Hz, 2H, CH_2), 7.09 (s, 1H, Ar), 7.41 (m, 4H, Ar), 7.62 (m, 1H, Ar), 7.76 (d, *J*=6.9 Hz, 1H, Ar), 7.80–7.82 (m, 2H, Ar), 8.01 (d, *J*=6.9 Hz, 1H, Ar), 8.53 (s, 1H, Ar). ^{13}C NMR (75 MHz, $CDCl_3$): δ=24.3, 25.1, 30.2 (CH_2), 111.6 (CH), 118.8, 121.7 (C), 126.1 (CH), 126.5 (C), 127.7, 127.7, 128.4, 128.9, 129.4, 129.4, 129.7, 130.1, 130.4 (CH), 132.1, 133.6, 144.3, 147.6, 148.3, 164.1 (C). IR (ATR): $\tilde{\nu}$=2917, 1633, 1595, 1494 (w), 1438 (m), 1288, 1126 (w), 894, 771 (m), 747, 697 (s) cm^{-1}. GC–MS (EI, 70 eV): *m*/*z* (%)=336 (24, M^++1), 335 (100, M^+), 334 (74), 167 (15). HRMS (EI): calcd for $C_{23}H_{17}N_3$ $[M]^+$: 335.1414; Found: 335.1412.

*3.3.9. 7-Phenyl-1,2,3,4-tetrahydrobenzo[b]indazolo[3,2-f][1,6]naphthyridine (**5i**).* Starting with 2-(phenylethynyl)quinoline-3-carbaldehyde (**3a**) (150 mg, 0.58 mmol), sulfonohydrazide (186 mg, 1 mmol), cyclohexanone (**4i**) (0.094 mg, 0.96 mmol), AgOTf (10 mol %), K_3PO_4 (1.8 mmol) in EtOH (3 ml), **5i** was isolated after column chromatography (silica gel, *n*-heptane/EtOAc=12:1) as a yellowish solid (117 mg, 87%), mp=235–237 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ=1.84–1.86 (m, 4H, CH_2), 2.81 (t, *J*=6.9 Hz, 2H, CH_2), 3.01 (t, *J*=5.9 Hz, 2H, CH_2), 7.11 (s, 1H, Ar), 7.42–7.44 (m, 4H, Ar), 7.60–7.63 (m, 1H, Ar), 7.76 (d, *J*=8.3 Hz, 1H, Ar), 7.80–7.83 (m, 2H, Ar), 8.01 (d, *J*=8.1 Hz, 1H, Ar), 8.52 (s, 1H, Ar). ^{13}C NMR (75 MHz, $CDCl_3$): δ=22.9, 22.9, 23.3, 24.2 (CH_2), 112.2 (CH), 118.2, 118.6, 119.6 (C), 126.1 (CH), 126.4 (C), 127.9, 128.4, 128.4 (CH), 128.6 (C), 128.8, 129.6, 129.6, 129.7, 129.8, 130.0 (CH), 133.5, 143.4, 147.8, 151.8 (C). IR (ATR): $\tilde{\nu}$=2936, 1614, 1571 (w), 1449, 1351 (m), 1197 (w), 895, 766 (m), 742 (s), 611 (m) cm^{-1}. GC–MS (EI, 70 eV): *m*/*z* (%)=350 (25, M^++1), 349 (100, M^+), 348 (47), 321 (30). HRMS (EI): calcd for $C_{24}H_{19}N_3$ $[M]^+$: 349.1573. Found: 349.1570.

*3.3.10. 4-Methyl-7-phenyl-1,2,3,4-tetrahydrobenzo[b]indazolo[3,2-f][1,6]naphthyridine (**5j**).* Starting with 2-(phenylethynyl)quinoline-3-carbaldehyde (**3a**) (150 mg, 0.58 mmol), sulfonohydrazide (186 mg, 1 mmol), 2-methylcyclohexanone (**4j**) (108 mg, 0.96 mmol), AgOTf (10 mol %), K_3PO_4 (1.8 mmol) in EtOH (3 ml), **5j** was isolated after column chromatography (silica gel, *n*-heptane/EtOAc=9:1) as a yellowish solid (106 mg, 75%), mp=157–159 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ=1.35 (d, *J*=5.9 Hz, 3H, CH_3), 1.49–1.52 (m, 1H, CH), 1.80–1.81 (m, 1H, CH_2), 2.05–2.07 (m, 2H, CH_2), 3.03–3.05 (m, 3H, CH_2), 7.18 (s, 1H, Ar), 7.44–7.46 (m, 4H, Ar), 7.66–7.68 (m, 1H, Ar), 7.86 (d, *J*=9.5 Hz, 1H, Ar), 7.94–7.96 (m, 2H, Ar), 8.07 (d, *J*=8.34 Hz, 1H, Ar), 8.67 (s, 1H, Ar). ^{13}C NMR (75 MHz, $CDCl_3$): δ=20.4 (CH_3), 22.1, 23.3 (CH_2), 29.8 (CH), 31.9 (CH_2), 112.1 (CH), 118.2, 118.6, 119.6 (C), 126.1 (CH), 126.4 (C), 127.9, 128.4, 128.4, 128.6, 128.8, 128.9, 129.5 (CH), 129.6 (C), 129.7, 130.0 (CH), 133.4, 143.4, 147.9151.8 (C). IR (ATR) $\tilde{\nu}$=2846, 1613, 1567 (w), 1486, 1349 (m), 1138, 895, 856, 765 (m), 742, 694 (s), 611 (m) cm^{-1}. GC–MS (EI, 70 eV): *m*/*z* (%)=364 (28, M^++1), 363 (100, M^+), 362 (28), 334 (25). HRMS (EI): calcd for $C_{25}H_{21}N_3$ $[M]^+$: 363.1730. Found: 363.1727.

*3.3.11. 7-Phenyl-11,12,13,14-tetrahydro-10H-benzo[b]cyclopenta[3,4]pyrazolo[5,1-f][1,6]-naphthyridine (**5k**).* Starting with 2-(phenylethynyl)quinoline-3-carbaldehyde (**3a**) (150 mg, 0.58 mmol), sulfonohydrazide (186 mg, 1 mmol), cycloheptanone (**4k**) (108 mg, 0.96 mmol), AgOTf (10 mol %), K_3PO_4 (1.8 mmol) in EtOH (3 ml), **5k** was isolated after column chromatography (silica gel, *n*-heptane/EtOAc=9:1) as a yellowish solid (89 mg, 63%), mp=205–207 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ=1.70–1.72 (m, 2H, CH_2), 1.85–1.87 (m, 4H, CH_2), 2.89–2.92 (m, 2H, CH_2), 3.22–3.24 (m, 2H, CH_2), 7.11 (s, 1H, Ar), 7.42–7.44 (m, 4H, Ar), 7.67–7.69 (m, 1H, Ar), 7.86–7.88 (m, 3H, Ar), 8.06 (d, *J*=8.1 Hz, 1H, Ar), 8.96 (s, 1H, Ar). ^{13}C NMR (75 MHz, $CDCl_3$): δ=26.2, 27.1, 28.4, 29.3, 31.5 (CH_2), 112.2 (CH), 118.9, 119.9 (C), 126.2 (CH), 126.3 (C), 128.1, 128.3, 128.3, 128.7, 129.6, 129.7, 129.7, 129.8, 130.2 (CH), 133.5, 133.6, 143.4, 147.8, 148.2, 156.8 (C). IR (ATR): $\tilde{\nu}$=2922 (m), 1632, 1614 (w), 1477, 1320 (m), 1125 (w), 849, 769 (m), 744, 692 (s) cm^{-1}. GC–MS (EI, 70 eV): *m*/*z* (%)=364 (26, M^++1), 363 (100, M^+), 362 (46), 334 (23). HRMS (EI): calcd for $C_{25}H_{21}N_3$ $[M]^+$: 363.1730. Found: 363.1732.

*3.3.12. 7-Phenyl-10,11,12,13,14,15-hexahydrobenzo[b]cyclopenta[3,4]pyrazolo[5,1-f][1,6]naphthyridine (**5l**).* Starting with 2-(phenylethynyl)quinoline-3-carbaldehyde (**3a**) (150 mg, 0.58 mmol), sulfonohydrazide (186 mg, 1 mmol), cycloctanone (**4l**) (121 mg, 0.96 mmol), AgOTf (10 mol %), K_3PO_4 (1.8 mmol) in EtOH (3 ml), **5l** was isolated after column chromatography (silica gel, *n*-heptane/EtOAc=9:1) as a yellowish solid (89 mg, 60%), mp=165–167 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ=1.37–1.39 (m, 2H, CH_2), 1.52 (p, *J*=6.8 Hz, 2H, CH_2), 1.69 (p, *J*=6.1 Hz, 2H, CH_2), 1.89 (p, *J*=6.1 Hz, 2H, CH_2), 2.88 (t, *J*=6.1 Hz, 2H, CH_2), 3.15 (t, *J*=6.1 Hz, 2H, CH_2), 7.11–7.14 (m, 1H, Ar), 7.43–7.45 (m, 4H, Ar), 7.65–7.68 (m, 1H, Ar), 7.88–7.90 (m, 3H, Ar), 8.04 (d, *J*=8.1 Hz, 1H, Ar), 8.79 (s, 1H, Ar). ^{13}C NMR (75 MHz, $CDCl_3$): δ=21.7, 24.6, 25.1, 25.8, 26.7, 30.0 (CH_2), 111.1 (CH), 115.0, 118.6 (C), 125.1 (CH), 125.4 (C), 127.0, 127.3, 127.3, 127.8, 128.4, 128.6, 128.7, 128.7, 129.1 (CH), 132.5, 132.6, 142.4, 146.8, 146.9, 154.4 (C). IR (ATR): $\tilde{\nu}$=3054, 2845, 1633, 1568 (w), 1483, 1438, 1353 (m), 1255, 899 (w), 840 (m), 748, 693 (s), 610 (m) cm^{-1}. GC–MS (EI, 70 eV): *m*/*z* (%)=378 (29, M^++1), 377 (100, M^+), 376 (21), 349 (33), 334 (38). HRMS (EI): calcd for $C_{26}H_{23}N_3$ $[M]^+$: 337.1886. Found: 337.1889.

*3.3.13. Methyl-2-methyl-5-phenylbenzo[b]pyrazolo[5,1-f][1,6]naphthyridine-1-carboxylate (**5m**).* Starting with 2-(phenylethynyl) quinoline-3-carbaldehyde (**3a**) (150 mg, 0.58 mmol), sulfonohydrazide (186 mg, 1.0 mmol), methyl acetoacetate (**4m**) (111 mg, 0.96 mmol), AgOTf (10 mol %), K_3PO_4 (1.8 mmol) in EtOH (3 ml), **5m** was isolated after column chromatography (silica gel, *n*-heptane/EtOAc=9:1) as a yellowish solid (120 mg, 84%), mp=87–89 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ=2.58 (s, 3H, CH_3), 3.98 (s, 3H, OCH_3), 7.50–753 (m, 5H, Ar), 7.76–7.78 (m, 1H, Ar), 7.84–7.87 (m, 2H, Ar), 8.10 (q, *J*=7.7 Hz, 2H, Ar), 10.59 (s, 1H, Ar). ^{13}C NMR (75 MHz, $CDCl_3$): δ=14.9, 50.7 (CH_3), 107.9 (C), 114.4 (CH), 116.8, 125.4 (C), 125.5, 125.5, 127.3, 127.3, 128.4, 128.4, 128.9, 128.9, 130.5 (CH), 131.9 (C), 35.4 (CH), 139.2, 141.6, 146.3, 147.8, 152.8, 164.4 (C). IR (ATR): $\tilde{\nu}$=2924 (w), 1704 (m), 1616 (w), 1533 (m), 1493 (w), 1448, 1257, 1190 (m), 1081 (s), 855 (m), 744, 688 (s), 628 (m) cm^{-1}. GC–MS (EI, 70 eV): *m*/*z* (%)=368 (24, M^++1), 367 (100, M^+), 366 (62), 336 (33): HRMS (EI): calcd for $C_{23}H_{17}N_3O_2$ $[M]^+$: 367.1315. Found: 367.1314.

*3.3.14. 1-Methyl-2,5-diphenylbenzo[b]pyrazolo[5,1-f][1,6]naphthyridine (**5n**).* Starting with 2-(phenylethynyl)quinoline-3-carbaldehyde (**3a**) (150 mg, 0.58 mmol), sulfonohydrazide (186 mg, 1.0 mmol),

propiophenone (**4n**) (129 mg, 0.96 mmol), AgOTf (10 mol %), K_3PO_4 (1.8 mmol) in EtOH (3 ml), **5n** was isolated after column chromatography (silica gel, *n*-heptane/EtOAc=9:1) as a yellowish solid (96 mg, 64%), mp=208–210 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ=2.69 (s, 3H, CH_3), 7.21 (s, 1H, Ar), 7.36–7.38 (m, 7H, Ar), 7.62–7.66 (m, 3H, Ar), 7.85 (d, *J*=8.1 Hz, 1H, Ar), 7.96–7.99 (m, 2H, Ar), 8.04 (d, *J*=8.7 Hz, 1H, Ar), 8.81 (s, 1H, Ar). ^{13}C NMR (75 MHz, $CDCl_3$): δ=11.9 (CH_3), 111.3 (CH), 118.3, 119.8, 126.3 (C), 126.3, 128.1, 128.3, 128.3, 128.5, 128.5, 128.9, 128.9, 129.2, 129.2, 129.7, 129.7, 129.8, 129.8, 130.3 (CH), 133.2, 135.2, 143.2, 147.8, 147.9, 152.9, 171.2 (C). IR (ATR): $\tilde{\nu}$=3053, 1613, 1555, 1493 (w), 1467, 1327 (m), 1173 (w), 1020, 913, 783 (m), 744, 696 (s) cm^{-1}. GC–MS (EI, 70 eV): *m*/*z* (%)=386 (26, M^++1), 385 (100, M^+), 384 (76), 281 (21). HRMS (EI): calcd for $C_{27}H_{19}N_3$ $[M]^+$: 385.1574. Found: 385.1576.

*3.3.15. 2-(4-Methoxyphenyl)-5-phenylbenzo[b]pyrazolo[5,1-f][1,6]naphthyridine (**5o**).* Starting with 2-(phenylethynyl)quinoline-3-carbaldehyde (**3a**) (150 mg, 0.58 mmol), sulfonohydrazide (186 mg, 1 mmol), *p*-methoxyacetophenone (**4o**) (144 mg, 0.96 mmol), AgOTf (10 mol %), K_3PO_4 (1.8 mmol) in EtOH (3 ml), **5o** was isolated after column chromatography (silica gel, *n*-heptane/EtOAc=9:1) as a yellowish solid (97 mg, 62%), mp=195–197 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ=3.91 (s, 3H, OCH_3), 7.01 (d, *J*=8.2 Hz, 2H, Ar), 7.21 (s, 1H, Ar), 7.41 (s, 1H, Ar), 7.52 (s, 1H, Ar), 7.59–7.61 (m, 4H, Ar), 7.81–7.82 (m, 1H, Ar), 7.98–8.1 (m, 2H, Ar), 8.04 (d, *J*=8.1 Hz, 1H, Ar), 8.10–8.13 (m, 2H, Ar), 8.23 (d, *J*=8.1 Hz, 1H, Ar), 8.92 (s, 1H, Ar). ^{13}C NMR (75 MHz, $CDCl_3$): δ=55.3 (OCH_3), 97.3, 113.1, 114.1, 114.1 (CH), 118.1, 125.6 (C), 126.4 (CH), 126.6 (C), 127.6, 127.6, 127.9, 128.2, 128.2, 129.1, 129.8, 129.8, 129.8, 130.5, 130.5 (CH), 133.1, 139.7, 143.2, 147.3, 148.8, 152.7, 159.9 (C). IR (ATR): $\tilde{\nu}$=2924 (w), 1704 (m), 1616 (w), 1533 (m), 1493 (w), 1448, 1257, 1190 (m), 1081 (s), 855 (m), 744, 688 (s), 628 (m) cm^{-1}. GC–MS (EI, 70 eV): *m*/*z* (%)=402 (29, M^++1), 401 (100, M^+), 400 (39). HRMS (EI): calcd for $C_{27}H_{19}N_3O$ $[M]^+$: 401.1516. Found: 401.1516.

*3.3.16. 2-Methyl-5-pentylbenzo[b]pyrazolo[5,1-f][1,6]naphthyridine (**5p**).* Starting with 2-(hept-1-yn-1-yl)quinoline-3-carbaldehyde, (**3b**) (98 mg, 0.39 mmol), sulfonohydrazide (75 mg, 0.40 mmol), acetone (**4f**) (0.046 mg, 0.8 mmol), AgOTf (10 mol %), K_3PO_4 (255 mg, 1.17 mmol) in EtOH (3 ml), **5p** was isolated after column chromatography (silica gel, *n*-heptane/EtOAc=9:1) as a yellowish solid (84 mg, 72%), mp=95–97 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ=0.89 (t, *J*=7.1 Hz, 3H, CH_3), 1.39–142 (m, 4H, CH_2), 1.88 (dd, *J*=8.1, 7.1 Hz, 2H, CH_2), 2.49 (s, 3H, CH_3), 3.12 (t, *J*=8.1 Hz, 2H, CH_2), 6.89 (s, 1H, Ar), 6.99 (s, 1H, Ar), 7.47 (t, *J*=7.1 Hz, 1H, Ar), 7.71 (t, *J*=7.1 Hz, 1H, Ar), 7.86 (d, *J*=8.1 Hz, 1H, Ar), 8.11 (d, *J*=8.1 Hz, 1H, Ar), 8.65 (s, 1H, Ar). ^{13}C NMR (75 MHz, $CDCl_3$): δ=14.0, 14.2 (CH_3), 22.6, 26.3, 30.8, 31.5 (CH_2), 100.4, 109.3 (CH), 125.4 (C), 126.0 (CH), 126.2 (C), 127.9, 128.9, 130.3, 130.5 (CH), 138.5, 144.9, 147.3, 148.5, 150.8 (C). IR (ATR) $\tilde{\nu}$=3051, 1808 (w), 1639 (s), 1615, 1497 (m), 1326 (s), 1180, 1077 (w), 973, 903 (m), 754, 732 (s), 587 (m) cm^{-1}. GC–MS (EI, 70 eV): *m*/*z* (%)=304 (10, M^++1), 303 (45, M^+), 302 (17), 248 (22), 247 (100). HRMS (EI): calcd for $C_{20}H_{21}N_3$ [M]+: 303.1730. Found: 303.1727.

*3.3.17. 5-Pentyl-1-propylbenzo[b]pyrazolo[5,1-f][1,6]naphthyridine (**5q**).* Starting with 2-(hept-1-yn-1-yl)quinoline-3-carbaldehyde (**3b**) (98 mg, 0.39 mmol), sulfonohydrazide (75 mg, 0.40 mmol), pentanal (**4a**) (0.069 mg, 0.8 mmol), AgOTf (10 mol %), K_3PO_4 (255 mg, 1.17 mmol) in EtOH (3 ml), **5q** was isolated after column chromatography (silica gel, *n*-heptane/EtOAc=9:1) as a yellowish solid (93 mg, 72%), mp=88–90 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ=0.81 (t, *J*=7.1 Hz, 3H, CH_3), 1.11 (t, *J*=7.1 Hz, 3H, CH_3), 1.38–1.40 (m, 4H, CH_2), 1.78–1.81 (m, 4H, CH_2), 2.89 (t, *J*=7.1 Hz, 2H, CH_2), 3.08 (t, *J*=7.1 Hz, 2H, CH_2), 7.01 (s, 1H, Ar), 7.43–7.46 (m, 1H, Ar), 7.64–7.67 (m, 1H, Ar), 7.78 (s, 1H, Ar), 7.81 (d, *J*=8.1 Hz, 1H, Ar), 8.01 (d, *J*=8.1 Hz, 1H, Ar), 8.72 (s, 1H, Ar). ^{13}C NMR (75 MHz, $CDCl_3$): δ=14.0, 14.2 (CH_3), 22.2, 22.5, 26.5, 28.1, 30.9, 31.5 (CH_2), 110.3 (CH), 118.8, 119.3 (C), 126.0 (CH), 126.2 (C), 128.1, 128.7, 130.1, 130.2 (CH), 132.8 (C), 141.1 (CH), 145.1, 147.6, 147.7 (C). IR (ATR): $\tilde{\nu}$=3099 (w), 2927 (m), 1614, 1494 (w), 1462, 1333 (m), 1192, 986 (w), 899, 853, 752, 647 (s) cm^{-1}. GC–MS (EI, 70 eV): *m*/*z* (%)=332 (20, M^++1), 331 (86, M^+), 330 (48), 303 (24), 302 (100), 288 (17). HRMS (EI): calcd for $C_{22}H_{25}N_3$ $[M]^+$: 331.2039. Found: 331.2039.

*3.3.18. 7-Pentyl-1,2,3,4-tetrahydrobenzo[b]indazolo[3,2-f][1,6]naphthyridine (**5r**).* Starting with 2-(hept-1-yn-1-yl)quinoline-3-carbaldehyde (**3b**) (98 mg, 0.39 mmol), sulfonohydrazide (75 mg, 0.40 mmol), cyclohexanone (**4i**) (0.078 mg, 0.8 mmol), AgOTf (10 mol %), K_3PO_4 (255 mg, 1.17 mmol) EtOH (3 ml), **5r** was isolated after column chromatography (silica gel, *n*-heptane/EtOAc=9:1) as a yellowish solid (105 mg, 66%), mp=194–196 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ=0.81 (t, *J*=7.1 Hz, 3H, CH_3), 1.39–1.42 (m, 4H, CH_2), 1.88–1.90 (m, 6H, CH_2), 2.89 (t, *J*=5.1 Hz, 2H, CH_2), 3.01–3.06 (m, 4H, CH_2), 6.97–7.01 (m, 1H, Ar), 7.35–7.43 (m, 1H, Ar), 7.67–7.71 (m, 1H, Ar), 7.81 (d, *J*=8.1 Hz, 1H, Ar), 8.1 (d, *J*=8.1 Hz, 1H, Ar), 8.6 (s, 1H, Ar). ^{13}C NMR (75 MHz, $CDCl_3$): δ=14.0 (CH_3), 22.6 (CH_2), 22.9, 23.0, 23.3, 24.0, 26.4, 30.8, 31.5 (CH_2), 77.4, 108.9 (CH), 113.4, 119.2 (C), 125.8 (CH), 126.2 (C), 127.9, 128.7, 130.0 (CH), 132.8, 145.2, 147.5, 147.7, 151.4 (C). IR (ATR): $\tilde{\nu}$=3054 (w), 2921, 1635, 1573 (m), 1538 (w), 1485 (s), 1391 (w), 1348 (s), 1129 (m), 977 (w), 855 (s), 787 (m), 759, 696 (s) cm^{-1}. GC–MS (EI, 70 eV): *m*/*z* (%)=344 (14, M^++1), 343 (56, M^+), 342 (39), 288 (24), 287 (100), 259 (30). HRMS (EI): calcd for $C_{23}H_{25}N_3$ $[M]^+$: 343.2043. Found: 343.2041.

*3.3.19. 3-Methyl-7-pentyl-1,2,3,4-tetrahydrobenzo[b]indazolo[3,2-f][1,6]naphthyridine (**5s**).* Starting with 2-(hept-1-yn-1-yl)quinolone-3-carbaldehyde (**3b**) (98 mg, 0.39 mmol), sulfonohydrazide (75 mg, 0.40 mmol), 3-methylcyclohexanone (**4p**) (0.096 mg, 0.8 mmol), AgOTf (10 mol %), K_3PO_4 (0.09 mg, 1.17 mmol) in EtOH (3 ml), **5s** was isolated after column chromatography (silica gel, *n*-heptane/EtOAc=9:1) as a yellowish solid (105 mg, 75%), mp=162–164 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ=1.03 (t, *J*=6.8 Hz, 3H, CH_3), 1.21 (d, *J*=6.8 Hz, 3H, CH_3), 1.48–1.51 (m, 5H, CH_2), 1.97–2.01 (m, 4H, CH_2), 2.53 (q, *J*=9.7 Hz, CH), 2.96–3.24 (m, 5H, CH_2), 7.01 (s, 1H, Ar), 7.48–7.53 (m, 1H, Ar), 7.71–7.75 (m, 1H, Ar), 7.88 (d, *J*=7.8 Hz, 1H, Ar), 8.11 (d, *J*=8.1 Hz, 1H, Ar), 8.6 (s, 1H, Ar). ^{13}C NMR (75 MHz, $CDCl_3$): δ=14.0, 21.6 (CH_3), 22.2, 22.6, 26.3 (CH_2), 29.3 (CH), 30.8, 31.4, 31.5, 32.2 (CH_2), 108.9 (CH), 112.9, 119.0 (C), 125.7, 127.8, 128.6, 129.9, 129.9 (CH), 132.6, 145.1, 147.6, 147.7, 151.5 (C). IR (ATR): $\tilde{\nu}$=3051 (w), 2922, 2851 (m), 1574 (w), 1486 (s), 1369 (m), 1319 (s), 1129 (m), 977 (w), 900 (m), 826 (w), 757 (s), 653 (m) cm^{-1}. GC–MS (EI, 70 eV): *m*/*z* (%)=358 (13, M^++1), 357 (57, M^+), 356 (39), 302 (25), 301 (100), 259 (25). HRMS (EI): calcd for $C_{24}H_{27}N_3$ $[M]^+$: 357.2200. Found: 357.2201.

*3.3.20. 6-Pentyl-2,3-dihydro-1H-benzo[b]cyclopenta[3,4]pyrazolo[5,1-f][1,6]naphthyridine (**5t**).* Starting with 2-(hept-1-yn-1-yl)quinolone-3-carbaldehyde **3b** (98 mg, 0.39 mmol), sulfonohydrazide (75 mg, 0.40 mmol), cyclopentanone (**4h**) (0.067 mg, 0.8 mmol), AgOTf (10 mol %), K_3PO_4 (255 mg, 1.17 mmol) in EtOH (3 ml), **5t** was isolated after column chromatography (silica gel, *n*-heptane/EtOAc=9:1) as a yellowish solid (97 mg, 76%), mp=152–154 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ=0.81 (t, *J*=7.1 Hz, 3H, CH_3), 1.42 (t, *J*=7.1 Hz, 6H, CH_2), 1.78–1.82 (m, 2H, CH_2), 2.58–2.62 (m, 2H, CH_2), 2.89–2.93 (m, 2H, CH_2), 2.97–3.03 (m, 2H, CH_2), 6.93 (s, 1H, Ar), 7.38–7.42 (m, 1H, Ar), 7.70–7.73 (m, 1H, Ar), 7.92 (d, *J*=8.1 Hz, 1H, Ar), 8.11 (d, *J*=8.1 Hz, 1H, Ar), 8.53 (s, 1H, Ar). ^{13}C NMR (75 MHz, $CDCl_3$): δ=11.2 (CH_3), 22.5, 24.2, 24.9, 26.5, 30.2, 30.3, 31.5 (CH_2), 77.4, 108.9 (CH), 113.4, 119.2 (C), 125.8 (CH), 126.2 (C), 127.9 (CH), 128.7 (CH), 130.0 (CH), 132.8, 145.2, 147.5, 147.7, 151.4 (C). IR (ATR): $\tilde{\nu}$=3050 (w), 2924, 1481 (m), 1349 (s), 1127, 971 (w), 902, 757 (s), 603 (m) cm^{-1}. GC–MS (EI, 70 eV): *m*/*z* (%)=330 (11, M^++1), 329 (55,

M^+), 328 (83), 273 (100), 272 (40). HRMS (EI): calcd for $C_{22}H_{23}N_3$ $[M]^+$: 329.1892. Found: 329.1895.

*3.3.21. 2-Ethyl-1-methyl-5-pentylbenzo[b]pyrazolo[5, 1-f][1,6]naphthyridine (**5u**).* Starting with 2-(hept-1-yn-1-yl)quinolone-3-carbaldehyde (**3b**) (98 mg, 0.39 mmol), sulfonohydrazide (75 mg, 0.40 mmol), 3-pentanone (**4g**) (0.069 mg, 0.8 mmol), AgOTf (10 mol %), K_3PO_4 (255 mg, 1.17 mmol) in EtOH (3 ml), **5u** was isolated after column chromatography (silica gel, *n*-heptane/EtOAc=9:1) as a yellowish solid (115 mg, 89%), mp=137–139 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ=0.87 (t, J=6.1 Hz, 3H, CH_3), 1.31 (t, J=7.1 Hz, 3H, CH_3), 1.42 (t, J=7.1 Hz, 8H, CH_2), 1.89–1.93 (m, 2H, CH_2), 2.62 (s, 3H, CH_3), 7.01 (s, 1H, Ar), 7.53 (t, J=8.1 Hz, 1H, Ar), 7.71 (t, J=8.1 Hz, 1H, Ar), 7.92 (d, J=8.1 Hz, 1H, Ar), 8.21 (d, J=8.1 Hz, 1H, Ar), 8.82 (s, 1H, Ar). ^{13}C NMR (75 MHz, $CDCl_3$): δ=10.6, 11.2, 13.9 (CH_3), 20.0, 22.5, 26.4, 30.8, 31.5 (CH_2), 77.4, 109.9 (CH), 116.4, 120.2 (C), 125.3 (CH), 126.7 (C), 127.5, 128.3, 131.2 (CH), 133.8, 146.2, 147.1, 147.9, 152.1 (C). IR (ATR): $\tilde{\nu}$=3053, 1613, 1555, 1493 (w), 1467, 1327 (m), 1173 (w), 1020, 913, 783 (m), 744, 696 (s) cm^{-1}. GC–MS (EI, 70 eV): *m*/*z* (%)=332 (12, M^++1), 331 (50, M^+), 330 (18), 276 (22), 274 (100). HRMS (EI): calcd for $C_{22}H_{25}N_3$ $[M]^+$: 331.2043. Found: 331.2041.

*3.3.22. 7-Cyclopropyl-4-methyl-1,2,3,4-tetrahydrobenzo[b]indazolo[3,2-f][1,6]naphthyridine (**5v**).* Starting with 2-(cyclopropylethynyl) quinoline-3-carbaldehyde (**3c**) (86 mg, 0.39 mmol), sulfonohydrazide (75 mg, 0.40 mmol), 3-methylcyclohexanone (**4j**) (0.096 mg, 0.8 mmol), AgOTf (10 mol %), K_3PO_4 (255 mg, 1.17 mmol) in EtOH (3 ml) of ethanol, **5v** was isolated after column chromatography (silica gel, *n*-heptane/EtOAc=9:1) as a yellowish solid (105 mg, 75%), mp=92–94 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ=0.87 (t, J=7.1 Hz, 3H, CH_3), 1.18–1.23 (m, 2H, CH_2), 1.37–1.42 (m, 6H), 1.85–1.94 (m, 2H, CH_2), 3.17 (t, J=7.6 Hz, 2H, CH_2), 7.11 (s, 1H, Ar), 7.47–7.53 (m, 1H, Ar), 7.67–7.72 (m, 1H, Ar), 7.91 (d, J=8.1 Hz, 1H, Ar), 8.11 (d, J=8.1 Hz, 1H, Ar), 8.81 (s, 1H, Ar). ^{13}C NMR (75 MHz, $CDCl_3$): δ=14.3 (CH_3), 22.8, 26.5, 30.0, 31.5, 31.8 (CH_2), 77.2, 100.6, 110.6 (CH), 117.5, 118.2, 126.3 (C), 126.7 (CH), 128.2, 128.3 (C), 129.2 (CH), 129.3 (C), 130.5, 130.8 (CH), 131.1, 138.1 (C), 141.4 (CH). IR (ATR): $\tilde{\nu}$=3050 (w), 2951 (m), 2926 (s), 1639, 1443 (m), 1332 (s), 1247 (w), 921, 740, 614, 528 (m) cm^{-1}. GC–MS (EI, 70 eV): *m*/*z* (%)= 327 (4, M^+), 312 (24), 299 (42), 286 (100). HRMS (EI): calcd for $C_{26}H_{17}N_3$ $[M]^+$:327.1735. Found: 327.1730.

*3.3.23. 5-Cyclopropyl-1-propylbenzo[b]pyrazolo[5,1-f][1,6]naphthyridine (**5w**).* Starting with 2-(cyclopropylethynyl)quinoline-3-carbaldehyde (**3c**) (86 mg, 0.39 mmol), sulfonohydrazide (75 mg, 0.40 mmol), pentanal (**4a**) (0.069 mg, 0.8 mmol), AgOTf (10 mol %), K_3PO_4 (255 mg, 1.17 mmol) in EtOH (3 ml), **5w** was isolated after column chromatography (silica gel, *n*-heptane/EtOAc=9:1) as a yellowish solid (87 mg, 74%), mp=227–229 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ=0.94–0.98 (m, 2H, CH_2), 1.11 (t, J=6.7 Hz, 3H, CH_3), 1.15–1.18 (m, 2H, CH_2), 1.78–1.83 (m, 2H, CH_2), 2.67–2.72 (m, 1H, CH), 3.01 (t, J=7.6 Hz, 2H, CH_2), 6.72 (s, 1H, Ar), 7.43 (t, J=7.6 Hz, 1H, Ar), 7.71 (t, J=8.1 Hz, 1H, Ar), 7.78–7.81 (m, 2H, Ar), 8.2 (d, J=7.9 Hz, 1H, Ar), 8.6 (s, 1H, Ar). ^{13}C NMR (75 MHz, $CDCl_3$): δ=8.1, 8.2 (CH_2), 11.3 (CH), 14.2 (CH_3), 22.2, 28.1 (CH_2), 106.8 (CH), 118.9, 119.0 (C), 126.0 (CH), 126.1 (C), 128.1, 128.6, 130.1, 130.2 (CH), 132.8 (C), 141.3 (CH), 146.8, 147.6, 147.8 (C). IR (ATR): $\tilde{\nu}$=2865 (m), 2819 (s), 2479 (m), 2387 (w), 1390 (s), 1158, 805 (m) cm^{-1}. GC–MS (EI, 70 eV): *m*/*z* (%)=302 (16, M^++1), 301 (74, M^+), 300 (25), 286 (32), 273 (22), 272 (100). HRMS (EI): calcd for $C_{20}H_{19}N_3$ $[M]^+$: 301.1570. Found: 301.1573.

*3.3.24. 7-Cyclopropyl-1,2,3,4-tetrahydrobenzo[b]indazolo[3,2-f][1,6]naphthyridine (**5x**).* Starting with 2-(cyclopropylethynyl)quinolone-3-carbaldehyde (**3c**) (86 mg, 0.39 mmol), sulfonohydrazide (75 mg, 0.40 mmol), cyclohexanone (**4i**) (0.078 mg, 0.8 mmol), AgOTf (10 mol %), K_3PO_4 (255 mg, 1.17 mmol) in EtOH (3 ml), **5x** was isolated after column chromatography (silica gel, *n*-heptane/EtOAc=9:1) as a yellowish solid (93 mg, 76%), mp=183–185 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ=0.93–0.97 (m, 2H, CH_2), 1.12–1.17 (m, 2H, CH_2), 1.87–1.93 (m, 4H, CH_2), 2.67–2.71 (m, 1H, CH), 2.89–2.92 (m, 2H, CH_2), 2.67–2.71 (m, 2H, CH_2), 6.59–6.62 (s, 1H, Ar), 7.41 (t, J=7.3 Hz, 1H, Ar), 7.62 (t, J=7.3 Hz, 1H, Ar), 7.72 (d, J=8.1 Hz, 1H, Ar), 7.91 (d, J=8.1 Hz, 1H, Ar), 8.53 (s, 1H, Ar). ^{13}C NMR (75 MHz, $CDCl_3$): δ=8.5, 8.6 (CH_2), 11.2 (CH), 22.8, 22.9, 23.2, 24.1 (CH_2), 104.9 (CH), 113.5, 118.8, 125.7 (C), 125.9, 127.9 (CH), 128.4 (C), 129.9, 130.0 (CH), 132.7, 147.0, 147.4, 147.7 (C), 151.5 (CH). IR (ATR): $\tilde{\nu}$=2930, 1614, 1557 (w), 1486 (m), 1200, 1048 (w), 970, 894 (m), 740 (s), 657, 624 (w) cm^{-1}. GC–MS (EI, 70 eV): *m*/*z* (%)=314 (22, M^++1), 313 (100, M^+), 312 (84), 298 (82). HRMS (EI): calcd for $C_{21}H_{19}N_3$ $[M]^+$: 313.1573. Found: 313.1571.

*3.3.25. 1-Propylbenzo[b]pyrazolo[5,1-f][1,6]naphthyridine (**5y**).* Starting with 2-((trimethylsilyl)ethynyl)quinoline-3-carbaldehyde (**3d**) (99 mg, 0.39 mmol), sulfonohydrazide (75 mg, 0.40 mmol), pentanal (**4a**) (0.067 mg, 0.8 mmol), AgOTf (10 mol %), K_3PO_4 (255 mg, 1.17 mmol) in EtOH (3 ml), **5y** was isolated after column chromatography (silica gel, *n*-heptane/EtOAc=9:1) as a yellowish solid (83 mg, 81%), mp=127–128 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ=1.11 (t, J=7.1 Hz, 3H, CH_3), 1.81 (dt, J=8.1, 7.1 Hz, 2H, CH_2), 3.02 (t, J=7.1 Hz, 2H, CH_2), 7.13 (d, J=8.1 Hz, 1H, Ar), 7.48–7.53 (m, 1H, Ar), 7.67–7.72 (m, 1H, Ar), 7.77 (s, 1H, Ar), 7.91 (d, J=8.1 Hz, 1H, Ar), 8.13 (d, J=7.4 Hz, 1H, Ar), 8.22 (d, J=6.9 Hz, 1H, Ar), 8.71 (s, 1H, Ar). ^{13}C NMR (75 MHz, $CDCl_3$): δ=14.2 (CH_3), 22.2, 28.0 (CH_2), 112.9 (CH), 118.8, 120.1, 126.5 (C), 126.6 (CH) 128.1 (CH), 129.0, 130.3, 130.5, 131.5 (CH), 132.5 (C), 142.0 (CH), 147.5, 147.6 (C). IR (ATR): $\tilde{\nu}$=3053, 1613, 1555, 1493 (w), 1467, 1327 (m), 1173 (w), 1020, 913, 783 (m), 744, 696 (s) cm^{-1}. GC–MS (EI, 70 eV): *m*/*z* (%)=262 (6, M^++1), 261 (31, M^+), 233 (19), 232 (100), 205 (11). HRMS (EI): calcd for $C_{26}H_{17}N_3$ $[M]^+$: 261.1266. Found: 261.1266.

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