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Synthesis, characterization and applications of densely functionalized pyridazines and fulvene-type compounds containing azulene moiety

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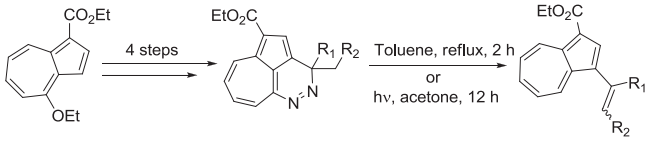
ABSTRACT

Ethyl 4-ethoxyazulene-1-carboxylate (**1**) is highly efficient and novel substrate for electrophilic substitution reactions. These derivatives (**2**–**4**) were treated with NH_2NH_2/$PhNHNH_2$ in ethanol to produce pyridazine, and fulvene derivatives with azulene frameworks (**5**, **6**, **17**, **19**) via intramolecular cyclization. The substrates **5**–**8**, **11**, and **19** were effectively converted into densely functionalized heterocyclic molecules via Vilsmeier–Haack, Friedel–Crafts, and Michael addition reactions.

1. Introduction

Azulene and its derivatives are interesting and structurally challenging carbocyclic moieties[1] because of the presence of azulene ring system as a centerpiece of number of bioactive natural products, such as orientalol F,[2a] purbinernoid,[2b] guaiane,[2c] pseudolaric acids A, B, F, and H,[2d] guanacastepene A, and heptemerone G,[2e] englerin A,[2f] (−)-9-deoxyenglerin A.[2g] Several azulene derivatives, in fact, have been known to exhibit various biological activities, such as insect anti-feeding agent,[3a] anti-fungal infections of skin and nails,[2d] anti-inflammatory agents,[3b] anti-oxidant therapeutics,[3c] and anti-microbial agents.[3d,e] Subsequently, azulenes and their derivatives have attracted the attention of chemists'[5a–c] due its abnormal properties and interesting modern applications.

The electrophilic substitution method is one of the most important methodologies for the functionalization of aromatic compounds.[4] There are several reports of electrophilic substitution reactions for functionalizing azulenes these including Vilsmeier–Haack formylations[6a–f] and Friedel–Crafts acylations,[7a,b] of azulene derivatives at 1- and/or 3-positions. Recently, we have reported the highly efficient intramolecular Friedel–Crafts type cyclization methodology on azulene derivatives at 3-position, and the applications of corresponding derivatives toward thermal and photo-chemical reactions (Scheme 1).[7b] In continuing of our research program[7b,8] in carbo- and heterocyclic molecules with azulene framework, we herein report the synthesis of pyridazine, and fulvene type of products with azulene moiety.



Scheme 1. Syntheses of vinyl azulene derivatives.[7b]

2. Results and discussion

Ethyl 4-ethoxyazulene-1-carboxylate (**1**) was prepared from commercially available tropolone in four steps.[8] Compound **1** was subjected to Vilsmeier–Haack formylation conditions ($POCl_3$/DMF, 0 °C, 3 h) to obtain ethyl 4-ethoxy-3-formylazulene-1-carboxylate (**2**), and with Friedel–Crafts acylation methodology (Ac_2O, $BF_3 \cdot Et_2O$, 0 °C, 2 h and $(CF_3CO)_2O/CH_2Cl_2$, room temperature,

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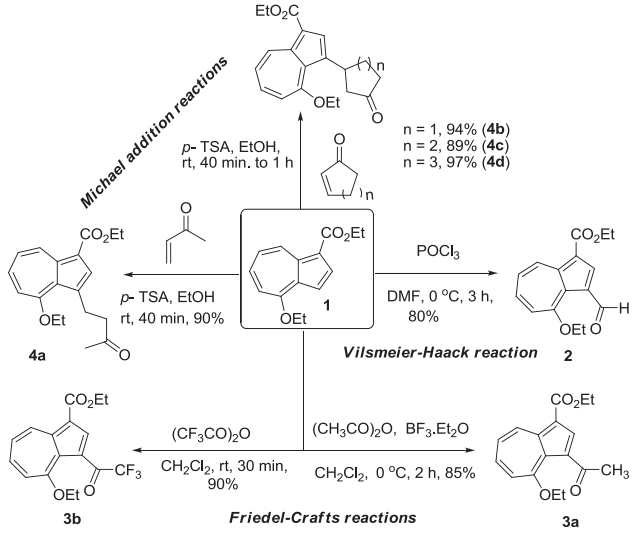
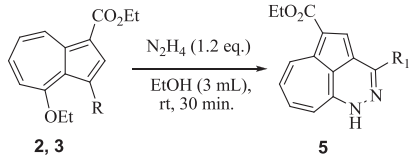
30 min) to produce ethyl 3-acetyl-4-ethoxyazulene-1-carboxylate (**3a**), and ethyl 4-ethoxy-3-(2,2,2-trifluoroacetyl)azulene-1-carboxylate (**3b**) with excellent yields (Scheme 2). We also extended our synthetic strategy toward the applications of Michael addition reactions.[9] The best results in this approach were obtained when ethyl 4-ethoxyazulene-1-carboxylate (**1**) was treated with methyl vinyl ketone (MVK) in the presence of *p*-toluenesulfonic acid (*p*-TSA) in ethanol at room temperature for 40 min, thus providing the desired ethyl 4-ethoxy-3-(3-oxobutyl)-azulene-1-carboxylate (**4a**), in 90% isolated yield (Scheme 2); the reaction proceeds more selectively at 3-position, which was confirmed from spectral analysis. To examine the scope of this reaction, we employed various activated cyclic enones, i.e., cyclopentenone, cyclohexenone, and cycloheptenone with the compound **1** (Scheme 2). A variety of cyclic enones have been proved to be very efficient substrates under these conditions.



Scheme 2. Selective Vilsmeier–Haack, Friedel–Crafts, and Michael addition reactions on ethyl 4-ethoxyazulene-1-carboxylate (**1**).

After successful syntheses of Vilsmeier–Haack and Friedel–-Crafts products, we found that ethyl 1*H*-azuleno[8,1-*cd*]-pyridazine-5-carboxylate (**5a**) was readily prepared in excellent yield (95%) from **2** and hydrazine in ethanol at room temperature for 30 min; the reaction presumably proceeded via a substitution reaction and a subsequent intramolecular condensation (Table 1, entry 1). Encouraged by these results, we successfully transformed representative Friedel–Crafts products **3a**,**b** into the desired ethyl 3-methyl-1*H*-azuleno[8,1-*cd*]pyridazine-5-carbo-xylate (**5b**) and ethyl 3-(trifluoromethyl)-1*H*-azuleno[8,1-*cd*]-pyridazine-5-carboxylate (**5c**) in excellent yields after purification by column chromatography (Table 1). The reactions apparently produced via a substitution

Table 1
Syntheses of azuleno[8,1-*cd*]pyridazine-5-carboxylate derivatives (**5**)[a]



Entry	Reactants **2**, **3**	R	Products **5**	R_1	Yield[b] (%)
1	**2**	CHO	**5a**	H	95
2	**3a**	$COCH_3$	**5b**	CH_3	92
3	**3b**	$COCF_3$	**5c**	CF_3	85

[a] All the reactions were carried out with 1 mmol scale of **2**, and **3**.
[b] Isolated yields after silica gel column chromatography.

followed by intramolecular condensation reactions. The structures of **5a**–**c** were confirmed from ^{1}H NMR, ^{13}C NMR, IR, and MS data analyses, while that of **5b** was further confirmed with single-crystal X-ray diffraction analysis (CCDC # 882109),[10] see Fig. 1 for the ORTEP diagram.

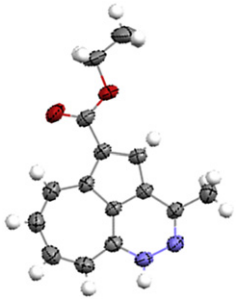
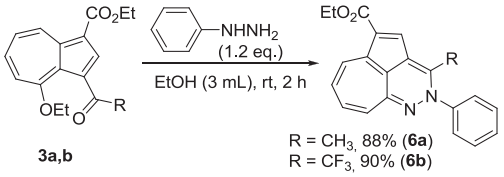


Fig. 1. ORTEP diagram of compound **5b**.

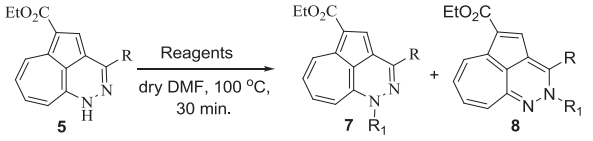
With a view to understand the generality of this methodology, we further investigated the reactions of **3a** and **3b** with phenyl hydrazine at room temperature for 2 h. Interestingly we obtained fulvene type products (**6a** and **6b**) with the π-electron delocalization within the ring system, in 88% and 90% yields, respectively (Scheme 3). All these products were well characterized from spectral analysis.



Scheme 3. Syntheses of fulvene type of products (**6a**, **b**).

Encouraged by these promising and interesting results, we further transformed **5a** and **5b**, by treatment with methyl/ethyl iodide with and/or without a base, into a mixture of *N*-alkylated pyridazines and/or fulvene type of products (**7a**–**d**, **8a**–**d**). We noticed that the compound **5c** did not convert to *N*-methylated or fulvene type of products (**7e**, **8e**) in the presence of methyl iodide in the absence of a base. Interestingly, with methyl iodide/ethyl iodide and NaH, we obtained exclusively the compounds **7e** (96%), and **7f** in 90% yield (Table 2); all these products were well characterized from the analysis of their spectral data. Particularly, with the help of

Table 2
N-Alkylation of azuleno[8,1-*cd*]pyridazine-5-caboxylate derivatives (**5**)[a]

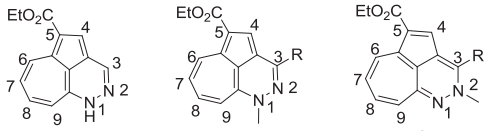


Entry	Reactants **5**	Reagents (1.2 equiv)	R_1	Products **7**/yield[b] (%)	Products **8**/yield[b] (%)
1	**5a**	CH_3I	CH_3	**7a**/15	**8a**/56
2	**5a**	CH_3CH_2I	CH_3CH_2	**7b**/–	**8b**/39
3	**5a**	CH_3CH_2I/NaH	CH_3CH_2	**7b**/35	**8b**/54
4	**5b**	CH_3I	CH_3	**7c**/13	**8c**/37
5	**5b**	CH_3CH_2I	CH_3CH_2	**7d**/14	**8d**/41
6	**5c**	CH_3I	CH_3	**7e**/–	**8e**/–
7	**5c**	CH_3I/NaH	CH_3	**7e**/96	**8e**/–
8	**5c**	CH_3CH_2I/NaH	CH_3CH_2	**7f**/90	**8f**/–

[a] All the reactions were carried out with 1 mmol scale of **5**.
[b] Isolated yields after silica gel column chromatography.

^{1}H NMR spectral data, easily we can differentiate *N*-alkylated pyridazines from fulvene type of products; principally, we noticed a large difference (~1.00 ppm) at the H6 proton chemical shift of the *N*-alkylated pyridazine and fulvene type of products. In comparison, the ^{1}H NMR spectral data of the compound **5a** is similar to that of the compounds **7**, but different from that of the compounds **8** (Table 3). We also obtained single crystals for compounds **7d**, **7f**, and **8b**, whose structure were further confirmed with single-crystal X-ray diffraction analysis (CCDC # 887649; 887650; 844733),[10] see Fig. 2 for the ORTEP diagrams.

Table 3
^{1}H NMR studies of compounds **5**, **7**, and **8**[a]



5a 7a 7c 8a 8c

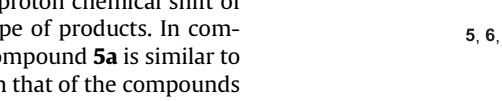
	5a	7a	7c	8a	8c
H3	7.77	7.68		7.47	
H4	7.05	7.21	7.21	6.96	6.88
H6[b]	8.02	8.25	8.30	7.37	7.37
H7	5.75	5.83	5.88	5.30	5.28
H8	6.53	6.59	6.62	5.87	5.85
H9	6.06	5.82	5.91	5.63	5.62

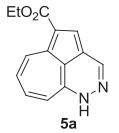
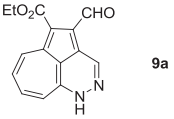
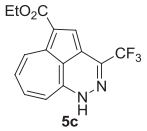
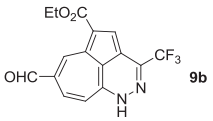
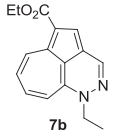
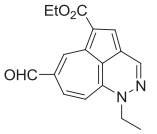
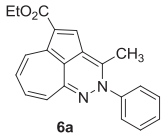
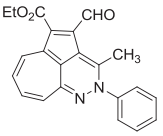
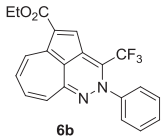
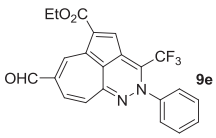
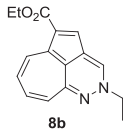
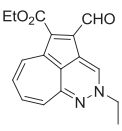
[a] ^{1}H NMR chemical shift in ppm.
[b] Large difference (~1.00 ppm) at the H6 proton chemical shift of the N-alkylated pyridazine and fulvene type of products.

After successful syntheses of various *N*-alkylated pyridazine derivatives, we focused our attention toward the synthetic applications of Vilsmeier–Haack formylation reactions on ethyl 1*H*-azuleno[8,1-*cd*]pyridazine-5-carboxylate (**5a**) and their various substituted products (**5c**, **6a**, **6b**, **7b**, **8b**). At first, for a model study we selected **5a**, which was treated with $POCl_3$ (1.2 equiv)/DMF (3 mL) at 0 °C for 10 min, and the reaction continued at 90 °C for 2 h, thus providing ethyl 4-formyl-1*H*-azuleno[8,1-*cd*]pyridazine-5-carboxylate (**9a**) in 81% isolated yield after purification by column chromatography (Table 4, entry 1). In order to understand the generality of this reaction, we subjected various substituted and *N*-alkylated ethyl azuleno[8,1-*cd*]-pyridazine-5-carboxylates (**5c**, **6a**, **6b**, **7b**, **8b**) into the desired chemoselectively substituted formyl azuleno[8,1-*cd*]pyridazine-5-carboxylates (**9b**–**f**) in excellent yields (Table 4, entries 2–6).

Alternatively, we have also obtained very promising and interesting results in one-pot operation with consecutive formation of products via Vilsmeier–Haack formylation, such as ethyl 4-formyl-2-

Table 4
Scope of the Vilsmeier–Haack formylation reaction on azuleno[8,1-*cd*]pyridazine-5-caboxylate derivatives (**5**, **6**, **7**, **8**)[a]



Entry	Reactants **5**, **6**, **7**, **8**	Products **9**	Yield[b] (%)
1			81
2			79
3			90
4			84
5			86
6			88

[a] All the reactions were carried out with 1 mmol scale of reactants.
[b] Isolated yields after silica gel column chromatography.

(prop-1-en-2-yl)-2*H*-azuleno[8,1-*cd*]pyridazine-5-carboxylate (**12**) and its derivative **13**, which were synthesized from ethyl 4-(2-(propan-2-ylidene)hydrazinyl)azulene-1-carboxylate (**11a**) and its derivative ethyl 4-(2-(4-ethoxy-4-oxobutan-2-ylidene)hydrazinyl) azulene-1-carboxylate (**11b**), which in turn were prepared from ethyl 4-hydrazinylazulene-1-carboxylate (**10**) and ethyl 4-ethoxyazulene-1-carboxylate (**1**) with 2.5 equiv of $POCl_3$/DMF

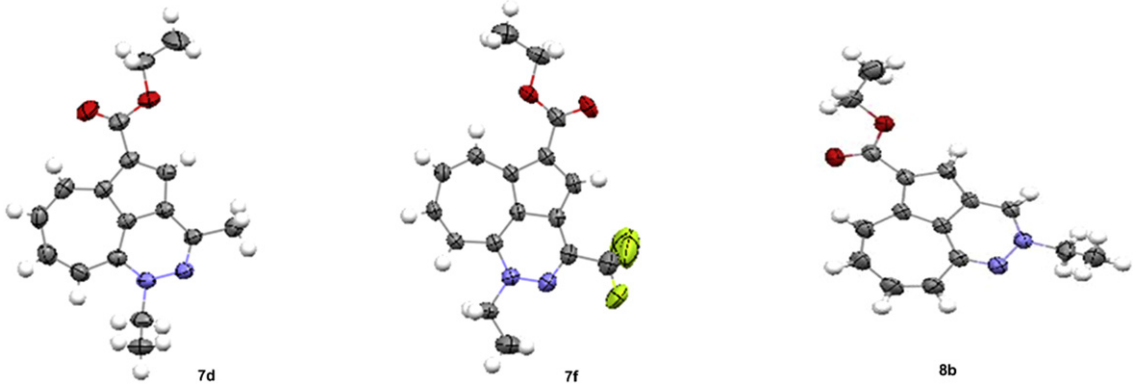
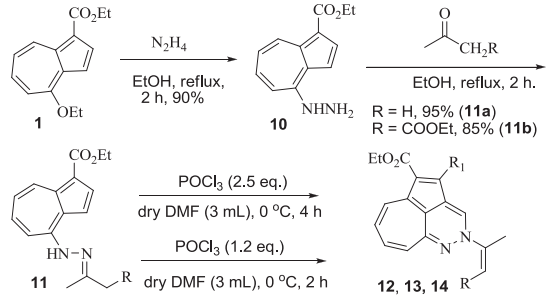


Fig. 2. ORTEP diagrams of compounds **7d**, **7f**, and **8b**.

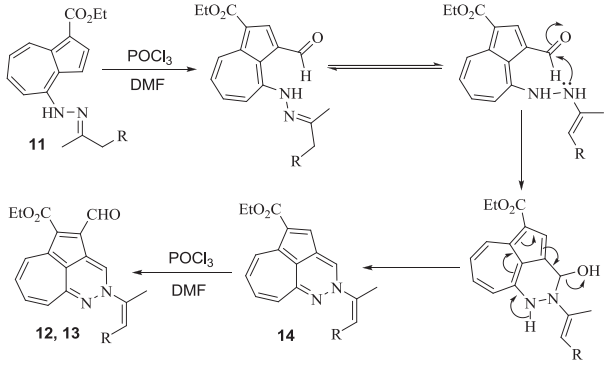
(3 mL) at 0 °C for 4 h. Interestingly, in the presence of 1.2 equiv of $POCl_3$/DMF (3 mL) at 0 °C for 2 h, ethyl 2-(4-ethoxy-4-oxobut-2-en-2-yl)-2*H*-azuleno[8,1-*cd*]pyridazine-5-carboxylate (**14**) was obtained in 85% isolated yield, presumably formed via the Vilsmeier–Haack formylation followed by cyclization (Scheme 4). The structures of **12**, **13**, and **14** were confirmed with spectral analyses. A plausible mechanism is presented in Scheme 5.



Entry	Reactants **11**	R	R_1	Products/ Yield[a] (%)
1	**11a**	H	CHO	**12**/82
2	**11b**	COOEt	CHO	**13**/78
3	**11b**	COOEt	H	**14**/85

[a] Isolated yields after silica gel column chromatography.

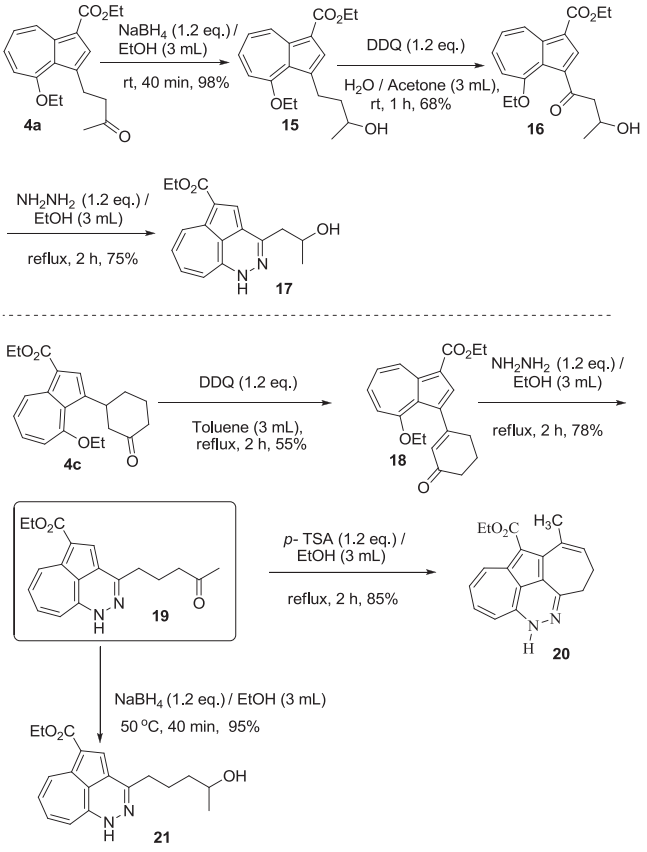
Scheme 4. Tandem Vilsmeier–Haack reactions on **11**.



Scheme 5. Plausible mechanism for the formation of Vilsmeier–Haack products (**12**, **13**, **14**).

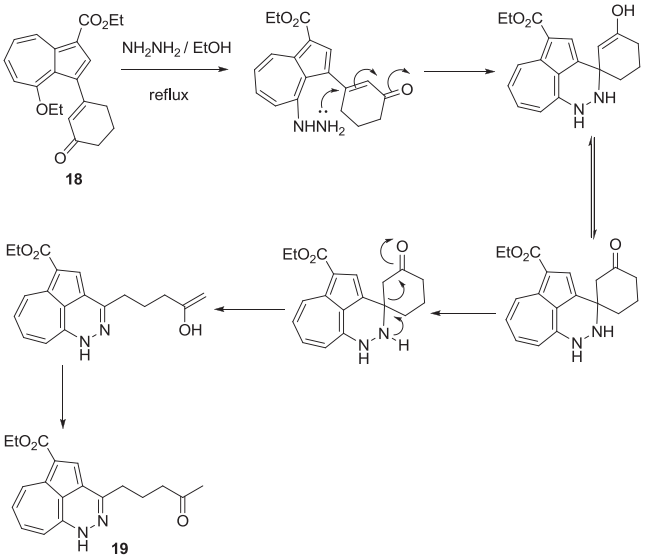
Subsequently, we focused our attention toward the syntheses of highly functionalized nitrogen heterocyclic molecules from the Michael adducts, which are readily prepared from ethyl 4-ethoxyazulene-1-carboxylate (**1**). The Michael adduct **4a** was treated with $NaBH_4$ in ethanol at room temperature for 40 min to obtain the compound **15** in 98% yield. Then upon oxidation with DDQ in presence of water/acetone, we accomplished the required key intermediate **16** for the formation of nitrogen heterocyclic molecule. Further, the compound **16** was subjected to hydrazine in ethanol under reflux for 2 h to attain ethyl (2-hydroxypropyl)-1*H*-azuleno[8,1-*cd*]pyridazine-5-carboxylate (**17**); the reaction apparently proceeded via a substitution reaction and a subsequent intramolecular condensation (Scheme 6).

Encouraged by these attractive results, we have extended the similar strategy to the compound **4c**, which was obtained from ethyl 4-ethoxyazulene-1-carboxylate (**1**) and cyclohexenone in presence of *p*-TSA in ethanol. Ethyl 4-ethoxy-3-(3-oxocyclo-hexyl) azulene-1-carboxylate (**4c**) was treated with DDQ in refluxing toluene for 2 h to obtain the dehydrogenated product **18**. After having



Scheme 6. Applications of Michael adducts **4a** and **4c**.

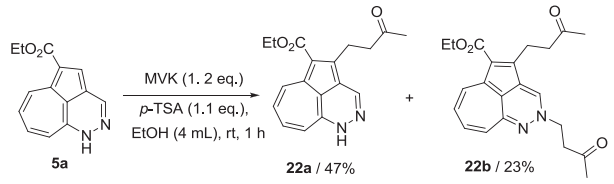
the compound **18** in hand, we subjected our synthetic methodology (NH_2NH_2/EtOH at reflux temperature for 2 h) to produce densely functionalized nitrogen heterocyclic molecule ethyl 3-(4-oxopentyl)-1*H*-azuleno[8,1-*cd*]pyridazine-5-carboxylate (**19**) in 78% yield (Scheme 6); the reaction presumably proceeded via substitution, intramolecular condensation, and a subsequent ring opening reactions (Scheme 7). The compound **19** is the key precursor for the intramolecular Friedel–Crafts reaction and the generation of secondary alcohols of ethyl 1*H*-azuleno[8,1-*cd*] pyridazine-5-carboxylate derivative. At first, the compound **19** was



Scheme 7. Plausible mechanism for the compound **19**.

readily converted for intramolecular Friedel–Crafts reaction in presence of *p*-TSA in ethanol to obtain heterocyclic molecule **20**. The product was well characterized with the spectral data analysis. Later, the compound **19** was further transformed into ethyl 3-(4-hydroxypentyl)-1*H*-azuleno[8,1-*cd*]pyridazine-5-carboxylate (**21**) in 95% yield in presence of $NaBH_4$ in EtOH (Scheme 6).

We also extended our Michael addition reaction strategy to ethyl 1*H*-azuleno[8,1-*cd*]pyridazine-5-carboxylate (**5a**), which was treated with MVK in presence of *p*-TSA in ethanol at room temperature for 1 h to attain ethyl 4-(3-oxobutyl)-1*H*-azuleno [8,1-*cd*] pyridazine-5-carboxylate (**22a**) as a major product in 47% isolated yield and **22b** as a minor product in 23% yield; the latter may be produced from the former via further Michael addition at the 2-position (Scheme 8). The structures of **22a** and **22b** were confirmed with ^{1}H NMR, ^{13}C NMR, IR, and MS data analyses, while that of **22a** was further confirmed with single-crystal X-ray diffraction analysis (CCDC # 844734),[10] see Fig. 3 for the ORTEP diagram.



Scheme 8. Michael addition reaction on ethyl 1*H*-azuleno-[8,1-*cd*]pyridazine-5-carboxylate (**5a**) with MVK.

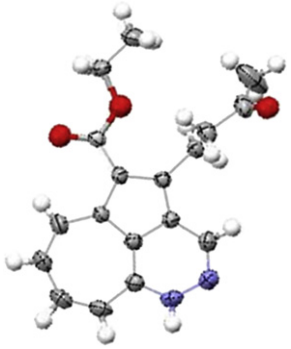


Fig. 3. ORTEP diagram of compound **22a**.

3. Conclusion

In summary, we have successfully developed a new substrate ethyl 4-ethoxyazulene-1-carboxylate (**1**) for the electrophilic substitution reactions. These derivatives (**2**–**4**) were effectively applied in the syntheses of pyridazine, and fulvene type of products with azulene moiety (**5**, **6**, **17**, **19**), and further applications were made toward the syntheses of densely functionalized heterocyclic molecules via the Vilsmeier–Haack, Friedel–Crafts, and Michael addition reactions. The utilization of this methodology for the synthesis of biological important molecules is in progress.

4. Experimental section

4.1. General experimental procedures

Unless stated otherwise, reagents were obtained from commercial sources and used without further purification. Thin layer chromatography (TLC) was performed by using Merck 5735 DC-Alufolien Kiesegel 60 F_{254}. Flash column chromatography was performed by using 230–400 mesh silica gel from Merck Art.9385 Kiesegel 60H. Except as otherwise indicated, yields were calculated after flash column chromatography. ^{1}H NMR and ^{13}C NMR spectra were recorded on Bruker ACE-300 M Hz FT-NMR. ^{19}F NMR spectra were recorded on a Bruker AMX-400 (376.5 MHz). Chemical shifts were reported as δ values referenced to $CDCl_3$. Coupling constants were reported in Hertz, and multiplicities are indicated as follows: s (singlet); d (doublet); dd (doublet of doublet); t (triplet); m (multiplet). IR spectra were recorded as thin film on KBr plates on a Jasco FT/IR-460 and reported in wave number (ν). Elemental analyses were recorded on a Thermo Finnigan Flash EA 1112 analyzer. Mass spectra are measured on Agilent 7890A GC-5975C MSD and Shimadzu-LCMS-2010 A mass spectrometers.

4.2. Procedure for the preparation of Vilsmeier–Haack product ethyl 4-ethoxy-3-formylazulene-1-carboxylate (2)

To a solution of ethyl 4-ethoxyazulene-1-carboxylate (**1**, 1 mmol, 0.244 g), in DMF (3 mL) at 0 °C was added $POCl_3$ (1.2 mmol, 0.1 mL) slowly for 10 min and the reaction continued for 3 h. Then the reaction mixture was diluted with water (10 mL), quenched with aqueous KOH solution, and was extracted with EtOAc. The combined organic layers were dried over $MgSO_4$, concentrated, and chromatographed on silica gel column chromatography (Hexane/EtOAc=2:1) to afford the compound **2**. Yield 80%; colorless solid (mp: 156–157 °C); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.40 (t, 3H, J=7.1 Hz), 1.65 (t, 3H, J=7.0 Hz), 4.37 (q, 2H, J=14.2 Hz), 4.50 (q, 2H, J=14.0 Hz), 7.39 (d, 1H, J=11.5 Hz), 7.50 (t, 1H, J=9.8 Hz), 7.86 (t, 1H, J=10.6 Hz), 8.77 (s, 1H), 9.80 (d, 1H, J=10.2 Hz), 10.85 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 14.4, 14.7, 60.0, 66.2, 115.0, 118.1, 126.1, 127.5, 131.6, 138.7, 138.8, 140.2, 142.4, 165.2, 165.7, 189.7; IR (KBr): ν 2360, 1684, 1644, 1235, 1214, 1050, 785 cm^{-1}. Anal. Calcd for $C_{16}H_{16}O_4$: C, 70.57; H, 5.92. Found: C, 70.51; H, 5.90.

*4.2.1. Procedure for the preparation of Friedel–Crafts product ethyl 3-acetyl-4-ethoxyazulene-1-carboxylate (**3a**).* To a stirred solution of ethyl 4-ethoxyazulene-1-carboxylate (**1**, 1 mmol, 0.244 g), in CH_2Cl_2 (3 mL) at 0 °C were added Ac_2O (1.0 mL) and $BF_3{\cdot}Et_2O$ (1.0 mL), and the reaction continued for 2 h. Then the reaction mixture was diluted with water (10 mL), quenched with aqueous $NaHCO_3$ solution, and was extracted with EtOAc. The combined organic layers were dried over $MgSO_4$, concentrated, and chromatographed on silica gel column chromatography (Hexane/EtOAc=2:1) to afford the compound **3a**. Yield 85%; red solid (mp: 124–125 °C); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.38 (t, 3H, J=7.1 Hz), 1.51 (t, 3H, J=7.1 Hz), 2.57 (s, 3H), 4.37 (m, 4H), 7.20 (d, 1H, J=11.1 Hz), 7.35 (t, 1H, J=10.2 Hz), 7.71–7.79 (m, 1H), 8.14 (s, 1H), 9.67 (d, 1H, J=10.2 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 14.0, 14.5, 32.5, 59.7, 66.0, 113.4, 116.0, 124.1, 124.9, 127.8, 129.7, 136.3, 138.5, 139.7, 164.1, 165.2, 201.9; IR (K Br): ν 2360, 1709, 1681, 1241, 1221, 1212, 1192, 742 cm^{-1}. Anal. Calcd for $C_{17}H_{18}O_4$: C, 71.31; H, 6.34. Found: C, 71.29; H, 6.33.

*4.2.2. Ethyl 4-ethoxy-3-(2,2,2-trifluoroacetyl)azulene-1-carboxylate (**3b**).* To a stirred solution of ethyl 4-ethoxyazulene-1-carboxylate (**1**, 1 mmol, 0.244 g), in CH_2Cl_2 (3 mL) at room temperature was added $(CF_3CO)_2O$ (1.0 mL), and the reaction continued for 2 h. Then the reaction mixture was diluted with water (10 mL), quenched with aqueous $NaHCO_3$ solution, and was extracted with EtOAc. The combined organic layers were dried over $MgSO_4$, concentrated, and chromatographed on silica gel column chromatography (Hexane/EtOAc=2:1) to afford the compound **3b**. Yield 90%; dark red solid (mp: 104–105 °C); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.41 (t, 3H, J=7.1 Hz), 1.51 (t, 3H, J=6.9 Hz), 4.35–4.47 (m, 4H), 7.35 (d, 1H, J=11.1 Hz), 7.48 (t, 1H, J=9.7 Hz), 7.87 (t, 1H, J=9.7 Hz), 8.33 (s, 1H), 9.76 (d, 1H, J=10.1 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 13.8, 14.5, 60.0, 66.4, 115.1, 115.5, 117.0, 117.8,

119.0, 125.9, 130.7, 138.1, 139.5, 140.3, 141.0, 164.9, 181.9; ^{19}F NMR (376.5 MHz, $CDCl_3$): δ −73.9; IR (KBr): ν 2360, 2341, 1709, 1681, 1241, 1221, 1212, 1192, 742 cm^{-1}. Anal. Calcd for $C_{17}H_{15}F_3O_4$: C, 60.00; H, 4.44. Found: C, 60.02; H, 4.46.

4.3. Typical procedure for the preparation of Michael addition products (4a–d)

To a stirred solution of ethyl 4-ethoxyazulene-1-carboxylate **1** (1 mmol, 0.244 g) in EtOH (4 mL) were added methyl vinyl ketone or cyclopentenone or cyclohexenone or cycloheptenone (1.2 mmol), and *p*-TSA (1.1 mmol, 0.189 g) at room temperature, and the reaction continued for 40 min (**4a**–**c**) to 1 h (**4d**). Aqueous KOH solution was added slowly to neutralize the reaction and the reaction mixture was extracted with EtOAc; the combined organic layers were dried over anhydrous $MgSO_4$, filtered, and stripped off solvent to give mixture of crude products were isolated by silica gel column chromatography.

*4.3.1. Ethyl 4-ethoxy-3-(3-oxobutyl) azulene-1-carboxylate (**4a**).* Yield 90%; purple solid (mp: 160–161 °C); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.43 (t, 3H, *J*=7.2 Hz), 1.57 (t, 3H, *J*=6.9 Hz), 2.16 (s, 3H), 2.87 (t, 2H, *J*=7.1 Hz), 3.46 (t, 2H, *J*=7.8 Hz), 4.33–4.44 (m, 4H), 7.01 (d, 1H, *J*=11.1 Hz), 7.16 (t, 1H, *J*=9.7 Hz), 7.60 (t, 1H, *J*=10.3 Hz), 7.96 (s, 1H), 9.60 (d, 1H, *J*=9.9 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 14.3, 14.6, 25.7, 29.8, 46.1, 59.4, 65.0, 111.4, 115.2, 121.5, 128.3, 128.7, 137.4, 137.8, 137.9, 139.5, 164.9, 165.3, 208.4; IR (KBr): ν 1671, 1109, 1043, 1083, 1003 cm^{-1}; GC–MS (*m*/*z*): 314 (M$^+$, 77), 257 (100), 229 (5), 201 (3), 183 (7). Anal. Calcd for $C_{19}H_{22}O_4$: C, 72.59; H, 7.05. Found: C, 72.62; H, 7.01.

*4.3.2. Ethyl 4-ethoxy-3-(3-oxocyclopentyl) azulene-1-carboxylate (**4b**).* Yield 94%; purple solid (mp: 157–158 °C); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.40 (t, 3H, *J*=6.9 Hz), 1.56 (t, 3H, *J*=6.9 Hz), 2.05–2.35 (m, 2H), 2.40–2.50 (m, 3H), 2.71 (dd, 1H, *J*=6.9, 10.8 Hz), 4.28–4.51 (m, 5H), 7.00 (d, 1H, *J*=11.1 Hz), 7.14 (t, 1H, *J*=9.6 Hz), 7.58 (t, 1H, *J*=10.3 Hz), 8.04 (s, 1H), 9.60 (d, 1H, *J*=9.9 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 14.5, 14.7, 31.8, 37.9, 38.6, 47.3, 59.7, 65.3, 111.9, 115.7, 122.1, 128.3, 131.1, 134.3, 137.8, 138.5, 139.9, 165.3, 165.4, 219.8; IR (KBr): ν 1682, 1175, 1076, 1039 cm^{-1}; GC–MS (*m*/*z*): 326 (M$^+$, 100), 297 (23), 270 (27), 253 (45), 225 (17), 197 (10). Anal. Calcd for $C_{20}H_{22}O_4$: C, 73.60; H, 6.79. Found: C, 73.62; H, 6.77.

*4.3.3. Ethyl 4-ethoxy-3-(3-oxocyclohexyl) azulene-1-carboxylate (**4c**).* Yield 89%; purple solid (mp: 165–166 °C); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.42 (t, 3H, *J*=6.9 Hz), 1.60 (t, 3H, *J*=6.9 Hz), 1.73–1.89 (m, 1H), 1.95–2.10 (m, 1H), 2.16–2.35 (m, 2H), 2.40–2.63 (m, 3H), 2.81 (d, 1H, *J*=15.3 Hz), 4.14–4.25 (m, 1H), 4.35–4.46 (m, 4H), 7.06 (d, 1H, *J*=11.1 Hz), 7.20 (t, 1H, *J*=9.9 Hz), 7.64 (t, 1H, *J*=10.3 Hz), 8.13 (s, 1H), 9.65 (d, 1H, *J*=9.9 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 14.6, 14.7, 26.1, 33.4, 39.8, 41.5, 50.7, 59.7, 65.4, 111.8, 116.0, 122.1, 127.5, 132.9, 134.6, 137.7, 138.6, 139.6, 165.3, 165.5, 211.9; IR (KBr): ν 1679, 1100, 1047 cm^{-1}; GC–MS (*m*/*z*): 340 (M$^+$, 100), 297 (30), 281 (23), 270 (13), 239 (13), 207 (15). Anal. Calcd for $C_{21}H_{24}O_4$: C, 74.09; H, 7.11. Found: C, 74.11; H, 7.09.

*4.3.4. Ethyl 4-ethoxy-3-(3-oxocycloheptyl) azulene-1-carboxylate (**4d**).* Yield 97%; purple solid (mp: 173–174 °C); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.41 (t, 3H, *J*=7.2 Hz), 1.54 (t, 3H, *J*=6.9 Hz), 1.70–1.88 (m, 2H), 1.95–2.10 (m, 2H), 2.31 (d, 2H, *J*=13.5 Hz), 2.55–2.65 (m, 2H), 2.78–3.00 (m, 2H), 4.18 (t, 1H, *J*=11.1 Hz), 4.26–4.42 (m, 4H), 6.96 (d, 1H, *J*=11.1 Hz), 7.12 (t, 1H, *J*=9.6 Hz), 7.54 (t, 1H, *J*=10.3 Hz), 8.04 (s, 1H), 9.60 (d, 1H, *J*=9.6 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 14.6, 14.7, 24.3, 29.8, 36.8, 40.0, 44.30, 52.8, 59.6, 65.3, 111.7, 116.0, 121.9, 126.9, 134.9, 135.4, 137.5, 138.4, 139.4, 165.3, 165.5, 214.2; IR (KBr): ν 1688, 1208, 1093, 1037 cm^{-1}; GC–MS (*m*/*z*): 354 (M$^+$, 100), 297 (32), 279 (22), 255 (15), 223 (19), 199 (7). Anal. Calcd for $C_{22}H_{26}O_4$: C, 74.55; H, 7.39. Found: C, 74.48; H, 7.39.

4.4. Typical procedure for the preparation of ethyl 1*H*-azuleno[8,1-*cd*]pyridazine-5-carboxylate derivatives (5 and 6)

To a solution of **2** or **3** (1 mmol), in ethanol (3 mL) was added NH_2NH_2/$PhNHNH_2$ (1.2 mmol) at room temperature and stirred for 30 min/2 h, the reaction mixture was quenched with water and extracted with EtOAc. The combined organic layers were dried over anhydrous $MgSO_4$, filtered, and stripped off solvent to give crude product, which was purified by silica gel column chromatography.

*4.4.1. Ethyl 1H-azuleno[8,1-cd]pyridazine-5-carboxylate (**5a**).* Yield 95%; green solid (mp: 146–147 °C); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.31 (t, 3H, *J*=3.5 Hz), 4.23 (q, 2H, *J*=6.0 Hz), 5.75 (t, 1H, *J*=9.8 Hz), 6.06 (d, 1H, *J*=11.7 Hz), 6.53 (dd, 1H, *J*=8.7, 11.7 Hz), 7.05 (s, 1H), 7.77 (s, 1H), 8.00 (d, 1H, *J*=11.1 Hz), 11.00 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 19.0, 64.2, 117.9, 123.2, 123.4, 124.9, 133.1, 138.9, 144.6, 146.6, 149.8, 158.6, 170.4; IR (KBr): ν 3270, 1665, 1442, 1422, 1118, 1082, 1034, 750 cm^{-1}; GC–MS (*m*/*z*): 240 (M$^+$, 100), 212 (80), 195 (40), 167 (30), 140 (20). Anal. Calcd for $C_{14}H_{12}N_2O_2$: C, 69.99; H, 5.03; N, 11.66. Found: C, 70.01; H, 5.00; N, 11.65.

*4.4.2. Ethyl 3-methyl-1H-azuleno[8,1-cd]pyridazine-5-carboxylate (**5b**).* Yield 92%; green solid (mp: 151–152 °C); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.38 (t, 3H, *J*=7.1 Hz), 2.18 (s, 3H), 4.33 (q, 2H, *J*=7.2 Hz), 5.80–5.90 (m, 2H), 6.47–6.56 (m, 1H), 7.18 (s, 1H), 8.15 (d, 1H, *J*=9.9 Hz), 9.08 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 14.5, 18.5, 59.8, 113.8, 117.1, 118.2, 119.1, 119.9, 129.0, 139.8, 140.9, 151.6, 152.4, 166.2; IR (KBr): ν 3205, 3050, 2977, 1693, 1430, 1230 cm^{-1}; GC–MS (*m*/*z*): 254 (M$^+$, 100), 226 (80), 209 (50), 181 (30), 152 (20). Anal. Calcd for $C_{15}H_{14}N_2O_2$: C, 70.85; H, 5.55; N, 11.02. Found: C, 70.83; H, 5.56; N, 11.00.

*4.4.2.1. Crystal data for **5b**.* Empirical formula=$C_{15}H_{14}N_2O_2$; formula weight=254.28; temperature=296 (2) K; wavelength=0.71073 Å; crystal system=triclinic; space group=*P*−1; unit cell dimensions, *a*=7.4962 (2) Å; *b*=9.9488 (2) Å; *c*=10.2979 (2) Å; α=63.5800 (10)°; β=86.1730 (10)°; γ=84.2410 (10)°; volume=684.10 (3) Å^3; *Z*=2; density (calculated)=1.322 Mg/m^3; absorption coefficient=0.093 mm^{-1}; *F*(000)=288; crystal size=0.02×0.02×0.02 mm^3; theta range for data collection=2.21–28.32°; index ranges=$-9\le h\le 9$, $-12\le k\le 13$, $-12\le l\le 13$; reflections collected=12,328; independent reflections=3386 [*R*(int)=0.0445]; completeness to theta=28.32°=99.7%; absorption correction=semi-empirical from equivalents; max. and min. transmission=0.9981 and 0.9981; refinement method=full-matrix least-squares on F^2; data/restraints/parameters=3386/0/191; goodness-of-fit on F^2=1.017; Final *R* indices [$I>2\sigma(I)$]=*R*1=0.0542, *wR*2=0.1156; *R* indices (all data)=*R*1=0.1352, *wR*2=0.1426; largest diff. peak and hole=0.164 and −0.168 e Å^{-3}. Detailed X-ray crystallographic data is available from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK (for compound **5b** CCDC # 882109).

*4.4.3. Ethyl 3-(trifluoromethyl)-1H-azuleno[8,1-cd]pyridazine-5-carboxylate (**5c**).* Yield 85%; green solid (mp: 233–234 °C); ^{1}H NMR (DMSO-d_6, 300 MHz): δ 1.38 (t, 3H, *J*=6.9 Hz), 4.29 (q, 2H, *J*=6.9 Hz), 5.96 (m, 1H), 6.23 (d, 1H, *J*=9.1 Hz), 6.70–6.78 (m, 1H), 7.19 (s, 1H), 8.15 (d, 1H, *J*=11.0 Hz); ^{13}C NMR (DMSO-d_6, 75 MHz): δ 14.3, 59.7, 111.1, 111.5, 118.5, 119.3, 121.8, 128.3, 135.8, 138.7, 142.8, 153.3, 164.7; ^{19}F NMR (376.5 MHz, $CDCl_3$): δ −70.2; IR (KBr): ν 3358, 3260, 3184, 3077, 2984, 1660, 1601 cm^{-1}; GC–MS (*m*/*z*): 308 (M$^+$,

100), 289 (60), 279 (16), 273 (15). Anal. Calcd for $C_{15}H_{11}F_3N_2O_2$: C, 58.45; H, 3.60; N, 9.09. Found: C, 58.41; H, 3.62; N, 9.10.

*4.4.4. Ethyl 3-methyl-2-phenyl-2H-azuleno[8,1-cd]pyridazine-5-carboxylate (**6a**, with $PhNHNH_2$).* Yield 88%; green solid (mp: 189–190 °C); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.37 (t, 3H, J=7.2 Hz), 2.13 (s, 3H), 4.32 (q, 2H, J=7.2 Hz), 5.41 (dd, 1H, J=8.1, 12.0 Hz), 5.79 (d, 1H, J=12.0 Hz), 5.96 (dd, 1H, J=8.1, 12.0 Hz), 7.16 (s, 1H), 7.32–7.55 (m, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 14.5, 16.9, 59.8, 112.6, 120.1, 121.3, 123.3, 125.1, 125.8, 128.7, 129.6, 129.8, 132.4, 136.1, 137.0, 142.4, 150.7, 159.6, 166.0; IR (KBr): ν 2296, 1680, 1610, 1066 cm^{-1}; GC–MS (m/z): 330 (100), 302 (60), 285 (24). Anal. Calcd for $C_{21}H_{18}N_2O_2$: C, 76.34; H, 5.49; N, 8.48. Found: C, 76.36; H, 5.50; N, 8.50.

*4.4.5. Ethyl 2-phenyl-3-(trifluoromethyl)-2H-azuleno[8,1-cd]-pyridazine-5-carboxylate (**6b**, with $PhNHNH_2$).* Yield 90%; yellow-green solid (mp: 202–203 °C); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.38 (t, 3H, J=7.1 Hz), 4.33 (q, 2H, J=7.2 Hz), 5.34 (dd, 1H, J=8.1, 12.0 Hz), 5.61 (d, 1H, J=12.0 Hz), 5.86 (dd, 1H, J=8.1, 12.0 Hz), 7.32–7.52 (m, 7H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 14.4, 60.2, 113.5 (q, J=34.5 Hz), 116.5, 117.9, 121.7, 122.9, 125.4, 125.9, 126.9, 128.8, 129.3, 130.1, 136.1, 138.5, 139.7 (q, J=283.2 Hz), 142.4, 161.1, 165; ^{19}F NMR (376.5 MHz, $CDCl_3$): δ −59.0; IR (KBr): ν 2293, 1686, 1600 cm^{-1}; GC–MS (m/z): 384 (100), 356 (45), 339 (20). Anal. Calcd for $C_{21}H_{15}F_3N_2O_2$: C, 65.62; H, 3.93; N, 7.29. Found: C, 65.65; H, 3.96; N, 7.30.

4.5. Typical procedure for the preparation of *N*-alkylated products (7 and 8)

To a solution of **5** (1 mmol), in DMF (3 mL) was added methyl iodide/ethyl iodide (1.2 mmol) at room temperature and refluxed at 100 °C for 30 min, then the reaction mixture was allowed to cool to room temperature. The reaction mixture was quenched with water and extracted with EtOAc. The combined organic layer was dried over anhydrous $MgSO_4$, filtered, and the solvent was removed to give crude product, which was purified by silica gel column chromatography.

*4.5.1. Ethyl 1-methyl-1H-azuleno[8,1-cd]pyridazine-5-carboxy-late (**7a**).* Yield 15%; dark blue solid (mp: 105–106 °C); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.38 (t, 3H, J=7.2 Hz), 3.41 (s, 3H), 4.33 (q, 2H, J=7.2 Hz), 5.82 (d, 1H, J=12.0 Hz), 5.83 (dd, 1H, J=8.7, 12.0 Hz), 6.59 (dd, 1H, J=8.7, 12.0 Hz), 7.21 (s, 1H), 7.68 (s, 1H), 8.25 (d, 1H, J=10.8 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 14.5, 43.1, 59.8, 113.9, 115.9, 117.6, 119.2, 119.3, 128.6, 136.3, 141.5, 142.2, 144.5, 153.2, 166.1; IR (KBr): ν 1673, 1107, 1083, 1049 cm^{-1}; GC–MS (m/z): 254 (100), 226 (83), 209 (39). Anal. Calcd for $C_{15}H_{14}N_2O_2$: C, 70.85; H, 5.55; N, 11.02. Found: C, 70.86; H, 5.53; N, 11.00.

*4.5.2. Ethyl 2-methyl-2H-azuleno[8,1-cd]pyridazine-5-carboxy-late (**8a**).* Yield 56%; green solid (mp: 109–110 °C); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.33 (t, 3H, J=7.2 Hz), 3.53 (s, 3H), 4.27 (q, 2H, J=7.2 Hz), 5.30 (dd, 1H, J=8.1, 11.5 Hz), 5.63 (d, 1H, J=12.2 Hz), 5.87 (ddd, 1H, J=0.8, 8.1, 12.2 Hz), 6.96 (s, 1H), 7.37 (d, 1H, J=11.5 Hz), 7.47 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 14.5, 47.5, 59.8, 111.8, 119.1, 121.3, 123.2, 124.6, 128.6, 133.8, 136.7, 137.7, 140.5, 161.7, 166.0; IR (KBr): ν 1669, 1110, 1083, 1013 cm^{-1}; GC–MS (m/z): 254 (100), 226 (90), 209 (22). Anal. Calcd for $C_{15}H_{14}N_2O_2$: C, 70.85; H, 5.55; N, 11.02. Found: C, 70.84; H, 5.57; N, 11.03.

*4.5.3. Ethyl 1-ethyl-1H-azuleno[8,1-cd]pyridazine-5-carboxy-late (**7b**).* Yield 35%; dark blue solid (mp: 138–139 °C); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.30 (t, 3H, J=7.2 Hz), 1.37 (t, 3H, J=7.2 Hz), 3.79 (q, 2H, J=7.2 Hz), 4.32 (q, 2H, J=6.9 Hz), 5.77–5.87 (m, 2H), 6.52–6.62 (m, 1H), 7.18 (s, 1H), 7.72 (s, 1H), 8.23 (d, 1H, J=10.5 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 12.2, 14.4, 49.8, 59.6, 113.6, 115.8, 117.6, 119.1, 119.4, 128.5, 136.3, 141.2, 141.9, 144.9, 152.4, 166.0; IR (KBr): ν 1670, 1109, 1093, 1030 cm^{-1}; LC–MS (m/z): 291.2 (M+23, 100), 270.2 (14.46), 269.2 (M+1, 100, 92.33), 240.2 (9.11). Anal. Calcd for $C_{16}H_{16}N_2O_2$: C, 71.62; H, 6.01; N, 10.44. Found: C, 71.60; H, 6.02; N, 10.39.

*4.5.4. Ethyl 2-ethyl-2H-azuleno[8,1-cd]pyridazine-5-carboxylate (**8b**).* Yield 54%; green solid (mp: 149–150 °C); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.33 (t, 3H, J=6.9 Hz), 1.41 (t, 3H, J=7.2 Hz), 3.70 (q, 2H, J=7.2 Hz), 4.28 (q, 2H, J=7.2 Hz), 5.27 (dd, 1H, J=3.3, 8.1 Hz), 5.64 (d, 1H, J=12.3 Hz), 5.85 (ddd, 1H, J=6.6, 8.4, 8.6 Hz), 6.96 (s, 1H), 7.36 (d, 1H, J=11.4 Hz), 7.51 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 14.4, 14.7, 55.7, 59.6, 111.3, 119.2, 121.0, 123.1, 124.2, 128.9, 134.0, 136.5, 137.4, 139.2, 161.9, 166.0; IR (KBr): ν 1671, 1115, 1043, 1063, 1018 cm^{-1}; LC–MS (m/z): 291.2 (M+23, 81.28), 279.2 (17.92), 271.3 (15.73), 270.1 (15.19), 269.2 (M+1, 100), 240.1 (19.95). Anal. Calcd for $C_{16}H_{16}N_2O_2$: C, 71.62; H, 6.01; N, 10.44. Found: C, 71.63; H, 6.00; N, 10.42.

*4.5.4.1. Crystal data for **8b**.* Empirical formula=$C_{16}H_{16}N_2O_2$; formula weight=268.31; temperature=296 (2) K; wavelength=0.71073 Å; crystal system=monoclinic; space group=P 1 21/c 1; unit cell dimensions, a=10.4209 (2) Å; b=14.9495 (2) Å; c=9.3605 (2) Å; α=90°; β=110.4120 (10)°; γ=90°; volume=1366.68 (4) Å^3; Z=4; density (calculated)=1.304 Mg/m^3; absorption coefficient=0.087 mm^{-1}; F(000)=568; crystal size=0.2×0.15×0.1 mm^3; theta range for data collection=2.09–28.29°; index ranges=$-12\leq h\leq 13$, $-19\leq k\leq 14$, $-12\leq l\leq 12$; reflections collected=12,024=independent reflections=3367 [R(int)=0.0441]; completeness to theta=28.29°=99.4%; absorption correction=semi-empirical from equivalents; refinement method=full-matrix least-squares on F^2; data/restraints/parameters=3367/0/184; goodness-of-fit on F^2=0.978; final R indices [I>2sigma(I)]=$R1$=0.0496, $wR2$=0.1060; R indices (all data)=$R1$=0.1298, $wR2$=0.1355; extinction coefficient=0.0043 (11); largest diff. peak and hole=0.167 and −0.154 e Å^{-3}. Detailed X-ray crystallographic data is available from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK (for compound **8b** CCDC # 844733).

4.5.5. Ethyl 1,3-dimethyl-1*H*-azuleno[8,1-*cd*]pyridazine-5-carbo-xylate (7c)

Yield 13%; dark blue solid (mp: 123–124 °C); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.39 (t, 3H, J=7.2 Hz), 2.18 (s, 3H), 3.44 (s, 3H), 4.35 (q, 2H, J=7.2 Hz), 5.88 (dd, 1H, J=8.7, 10.8 Hz), 5.91 (d, 1H, J=12.0 Hz), 6.62 (ddd, 1H, J=0.6, 8.7, 12.0 Hz), 7.21 (s, 1H), 8.30 (d, 1H, J=10.8 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 14.5, 18.4, 43.0, 59.7, 113.3, 115.8, 118.3, 118.8, 118.9, 128.7, 134.6, 140.9, 141.3, 151.8, 151.9, 166.2; IR (KBr): ν 1671, 1109, 1058, 1006 cm^{-1}; GC–MS (m/z): 268 (100), 240 (71), 223 (25). Anal. Calcd for $C_{16}H_{16}N_2O_2$: C, 71.62; H, 6.01; N, 10.44. Found: C, 71.60; H, 6.03; N, 10.40.

4.5.6. Ethyl 2,3-dimethyl-2*H*-azuleno[8,1-*cd*]pyridazine-5-carbo-xylate (8c)

Yield 37%; green solid (mp: 130–131 °C); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.33 (t, 3H, J=7.2 Hz), 2.17 (s, 3H), 3.47 (s, 3H), 4.26 (q, 2H, J=7.2 Hz), 5.28 (dd, 1H, J=7.8, 11.4 Hz), 5.62 (d, 1H, J=12.0 Hz), 5.85 (dd, 1H, J=7.8, 12.0 Hz), 6.87 (s, 1H), 7.37 (d, 1H, J=11.4 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 14.5, 15.6, 43.6, 59.6, 111.5, 120.4, 120.5, 121.8, 124.3, 128.7, 132.6, 136.1, 136.5, 150.0, 159.7, 166.2; IR (KBr): ν 1675, 1119, 1083, 1003 cm^{-1}; GC–MS (m/z): 268 (100), 240 (82), 223 (22). Anal. Calcd for $C_{16}H_{16}N_2O_2$: C, 71.62; H, 6.01; N, 10.44. Found: C, 71.59; H, 6.00; N, 10.44.

4.5.7. Ethyl 2-ethyl-3-methyl-2*H*-azuleno[8,1-*cd*]pyridazine-5-carboxylate (7d)

Yield 14%; dark blue solid (mp: 141–142 °C); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.31 (t, 3H, J=7.2 Hz), 1.39 (t, 3H, J=7.2 Hz), 2.19 (s, 3H), 3.84 (q, 2H, J=7.2 Hz), 4.35 (q, 2H, J=7.2 Hz), 5.87 (dd, 1H, J=8.7, 10.8 Hz), 5.95 (d, 1H, J=12.0 Hz), 6.61 (dd, 1H, J=8.7, 12.0 Hz), 7.19 (s, 1H), 8.29 (d, 1H, J=10.8 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 12.5, 14.6, 16.5, 49.8, 59.7, 113.1, 115.8, 118.4, 118.8, 118.9, 128.7, 134.7, 140.7, 141.1, 151.1, 152.3, 166.2; IR (KBr): ν 1672, 1116, 1086, 1002 cm^{-1}; GC–MS (m/z): 282 (100), 254 (45), 226 (71). Anal. Calcd for $C_{17}H_{18}N_2O_2$: C, 72.32; H, 6.43; N, 9.92. Found: C, 72.31; H, 6.43; N, 9.93.

4.5.7.1. Crystal data for ***7d****.* Empirical formula=$C_{17}H_{18}N_2O_2$; formula weight=282.33; temperature=298 (2) K; wavelength=0.71073 Å; crystal system=orthorhombic; space group=*P c a* 21; unit cell dimensions=a=22.6357 (11) Å; b=8.8938 (4) Å; c=7.2615 (3) Å; α=90°; β=90°; γ=90°; volume=1461.87 (11) Å^3; Z=4; density (calculated)=1.283 Mg/m^3; absorption coefficient=0.085 mm^{-1}; F(000)=600; crystal size=0.25×0.15×0.11 mm^3; theta range for data collection=2.29–28.30°; index ranges=$-30\leq h\leq 28$, $-11\leq k\leq 11$, $-9\leq l\leq 9$; reflections collected=9516; independent reflections=3626 [R(int)=0.0263]; completeness to theta=28.30°=99.9%; absorption correction=semi-empirical from equivalents; max. and min. transmission=0.9907 and 0.9790; refinement method=full-matrix least-squares on F^2; data/restraints/parameters=3626/1/193; goodness-of-fit on F^2=1.007; final R indices [I>2sigma(I)]=$R$1=0.0451, wR2=0.1127; R indices (all data)=$R$1=0.0617, wR2=0.1243; absolute structure parameter=0.3 (15); largest diff. peak and hole=0.190 and −0.195 e Å^{-3}. Detailed X-ray crystallographic data is available from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK (for compound **7d** CCDC # 887649).

4.5.8. Ethyl 2-ethyl-3-methyl-2*H*-azuleno[8,1-*cd*]pyridazine-5-carboxylate (8d)

Yield 41%; green solid (mp: 145–146 °C); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.33 (t, 3H, J=7.2 Hz), 1.34 (t, 3H, J=7.2 Hz), 2.25 (s, 3H), 3.79 (q, 2H, J=7.2 Hz), 4.27 (q, 2H, J=7.2 Hz), 5.30 (dd, 1H, J=8.1, 11.4 Hz), 5.68 (d, 1H, J=12.3 Hz), 5.87 (dd, 1H, J=8.1, 12.3 Hz), 6.94 (s, 1H), 7.39 (d, 1H, J=11.4 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 14.1, 14.5, 15.0, 50.9, 59.6, 111.5, 120.4, 120.5, 122.0, 124.3, 128.8, 132.5, 136.1, 136.5, 149.0, 160.1, 166.2; IR (KBr): ν 1676, 1109, 1093, 1010 cm^{-1}; GC–MS (m/z): 282 (100), 254 (44), 226 (79). Anal. Calcd for $C_{17}H_{18}N_2O_2$: C, 72.32; H, 6.43; N, 9.92. Found: C, 72.32; H, 6.44; N, 9.90.

4.5.9. Ethyl 1-methyl-3-(trifluoromethyl)-1*H*-azuleno[8,1-*cd*]pyridazine-5-carboxylate (7e)

Yield 96%; yellow-green solid (200–201 °C); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.39 (t, 3H, J=7.2 Hz), 3.43 (s, 3H), 4.35 (q, 2H, J=7.2 Hz), 5.81 (d, 1H, J=12.0 Hz), 5.94 (dd, 1H, J=1.5, 9.0 Hz), 6.65 (dd, 1H, J=3.3, 8.7 Hz), 7.37 (s, 1H), 8.30 (d, 1H, J=10.8 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 14.4, 43.5, 59.9, 112.0, 113.9, 115.1, 120.1, 120.3, 122.3, 129.3, 138.9, 141.4, 142.7, 152.8, 165.6; ^{19}F NMR (376.5 MHz, $CDCl_3$): δ −70.3; IR (KBr): ν 1670, 1109, 1080 cm^{-1}; LC–MS (m/z): 345.2 (M+23,100), 323.2 (M+1, 28.48), 309.2 (24.03). Anal. Calcd for $C_{16}H_{13}F_3N_2O_2$: C, 59.63; H, 4.07; N, 8.69. Found: C, 59.61; H, 4.09; N, 8.70.

4.5.10. Ethyl 1-ethyl-3-(trifluoromethyl)-1*H*-azuleno[8,1-*cd*]pyridazine-5-carboxylate (7f)

Yield 90%; yellow-green solid (207–208 °C); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.32 (t, 3H, J=7.2 Hz), 1.39 (t, 3H, J=7.2 Hz), 3.84 (q, 2H, J=7.2 Hz), 4.34 (q, 2H, J=7.2 Hz), 5.85–5.96 (m, 2H), 6.65 (dd, 1H, J=9.0, 9.8 Hz), 7.36 (s, 1H), 8.33 (d, 1H, J=10.8 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 12.0, 14.4, 50.4, 59.9, 77.4, 112.0, 113.6, 115.2, 118.7, 120.2, 122.3, 129.3, 139.0, 141.1, 142.6, 152.2, 165.6; ^{19}F NMR (376.5 MHz, $CDCl_3$): δ −73.3; IR (KBr): ν 1677, 1100, 1083, 1010 cm^{-1}; LC–MS (m/z): 359.2 (M+23, 100), 337.2 (M+1, 97.58), 309.2 (26.83), 264.1 (19.16). Anal. Calcd for $C_{17}H_{15}F_3N_2O_2$: C, 60.71; H, 4.50; N, 8.33. Found: C, 60.72; H, 4.48; N, 8.35.

4.5.10.1. Crystal data for ***7f****.* Empirical formula=$C_{17}H_{14}F_3N_2O_2$; formula weight=335.30; temperature=298 (2) K; wavelength=0.71073 Å; crystal system=monoclinic; space group=*P* 21/*m*; unit cell dimensions, a=10.4078 (3) Å; b=6.8160 (2) Å; c=10.9689 (4) Å; α=90°; β=92.845 (2)°; γ=90°; volume=777.17 (4) Å^3; Z=2; density (calculated)=1.433 Mg/m^3; absorption coefficient=0.119 mm^{-1}; F(000)=346; crystal size=0.15×0.13×0.11 mm^3; theta range for data collection=1.86–28.28°; index ranges=$-12\leq h\leq 13$, $-8\leq k\leq 9$, $-14\leq l\leq 13$; reflections collected=7477; independent reflections=2077 [R(int)=0.0431]; completeness to theta=28.28°=99.5%; absorption correction=semi-empirical from equivalents; max. and min. transmission=0.9870 and 0.9824; refinement method=full-matrix least-squares on F^2; data/restraints/parameters 2077/0/143; goodness-of-fit on F^2=1.052; Final R indices [I>2sigma(I)]=$R$1=0.0600, wR2=0.1586; R indices (all data)=$R$1=0.1236; wR2=0.1939; extinction coefficient=0.012 (5); largest diff. peak and hole=0.359 and −0.246 e Å^{-3}. Detailed X-ray crystallographic data is available from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK (for compound **7f** CCDC # 887650).

4.6. Typical procedure for the preparation of Vilsmeier–Haack products (9a–f, 12–14)

To a stirred solution of **5a** or **5c** or **6a** or **6b** or **7b′** or **8b** or **11a** or **11b** (1 mmol), in DMF (3 mL) at 0 °C was added $POCl_3$ (1.2 mmol, 0.1 mL) slowly for 10 min and the reaction continued at 90 °C/0 °C for 2 h. Then the reaction mixture was allowed to cool to room temperature and diluted with water (10 mL). The reaction mixture was quenched with aqueous KOH solution, and was extracted with EtOAc. The combined organic layers were dried over $MgSO_4$, concentrated, and chromatographed on silica gel column chromatography.

4.6.1. Ethyl 4-formyl-1*H*-azuleno[8,1-*cd*]pyridazine-5-carboxylate (9a)

Yield 81%; dark green solid (mp: 108–109 °C); ^{1}H NMR (CD_3COCD_3, 300 MHz): δ 1.39 (t, 3H, J=7.2 Hz), 4.39 (q, 2H, J=7.2 Hz), 5.95 (dd, 1H, J=8.7, 11.7 Hz), 6.31 (d, 1H, J=11.7 Hz), 6.67 (dd, 1H, J=8.7, 11.7 Hz), 7.93 (d, 1H, J=11.7 Hz), 8.77 (s, 1H), 10.6 (s, 1H); ^{13}C NMR (CD_3COCD_3, 75 MHz): δ 13.8, 60.2, 119.7, 120.2, 120.5, 121.9, 128.3, 128.7, 132.5, 138.8, 141.8, 144.7, 153.5, 165.0, 189.2; IR (KBr): ν 2308, 1702, 1104 cm^{-1}; GC–MS (m/z): 268 (48), 239 (100). Anal. Calcd for $C_{15}H_{12}N_2O_3$: C, 67.16; H, 4.51; N, 10.44. Found: C, 67.19; H, 4.50; N, 10.42.

4.6.2. Ethyl 7-formyl-3-(trifluoromethyl)-1*H*-azuleno[8,1-*cd*]-pyridazine-5-carboxylate (9b)

Yield 79%; yellow-green solid (mp: 126–127 °C); ^{1}H NMR (CD_3COCD_3, 300 MHz): δ 1.38 (t, 3H, J=7.2 Hz), 4.36 (q, 2H, J=7.2 Hz), 6.42 (d, 1H, J=12.0 Hz), 7.22 (dd, 1H, J=1.4, 12.0 Hz), 7.35 (q, 1H, J=1.8 Hz), 8.70 (d, 1H, J=1.4 Hz), 9.45 (s, 1H); ^{13}C NMR (CD_3COCD_3, 75 MHz): δ 13.7, 60.2, 114.4, 115.6, 117.7, 119.6, 122.3, 125.0, 129.6, 136.2, 137.9, 142.4, 148.9, 153.3, 164.4, 190.9; ^{19}F NMR (376.5 MHz, $CDCl_3$): δ −68.1; IR (KBr): ν 2310, 1706, 1104 cm^{-1}; GC–MS (m/z): 336 (100), 308 (49), 291 (40). Anal. Calcd for

$C_{16}H_{11}F_3N_2O_3$: C, 57.15; H, 3.30; N, 8.33. Found: C, 57.17; H, 3.32; N, 8.30.

4.6.3. Ethyl 1-ethyl-7-formyl-1*H*-azuleno[8,1-*cd*]pyridazine-5-carboxylate (9c)

Yield 90%; dark green color viscous liquid; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.35–1.44 (m, 6H), 3.98 (q, 2H, J=14.4 Hz), 4.37 (q, 2H, J=14.4 Hz), 6.03 (d, 1H, J=12.6 Hz), 7.25 (dd, 1H, J=11.4, 12.1 Hz), 7.34 (s, 1H), 7.95 (s, 1H), 8.74 (d, 1H, J=1.2 Hz), 9.43 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 12.7, 14.3, 50.9, 60.3, 115.1, 116.3, 121.1, 124.5, 127.5, 128.0, 136.1, 138.1, 145.1, 151.0, 152.1, 165.4, 191.5; IR (KBr): ν 2312, 1712, 1104 cm^{-1}; LC–MS (m/z): 297 (M+1, 59.81), 298 (11.22), 319 (M+23, 100), 320 (17.36). Anal. Calcd for $C_{17}H_{16}N_2O_3$: C, 68.91; H, 5.44; N, 9.45. Found: C, 68.94; H, 5.43; N, 9.45.

4.6.4. Ethyl 4-formyl-3-methyl-2-phenyl-2*H*-azuleno [8,1-*cd*]pyridazine-5-carboxylate (9d)

Yield 84%; green solid (mp: 207–208 °C); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.39 (t, 3H, J=7.2 Hz), 2.57 (s, 3H), 4.40 (q, 2H, J=7.2 Hz), 5.52 (dd, 1H, J=7.8, 11.7 Hz), 5.90 (d, 1H, J=12.3 Hz), 6.02 (dd, 1H, J=7.8, 12.3 Hz), 7.08 (d, 1H, J=11.7 Hz), 7.32–7.56 (m, 5H), 10.30 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 14.4, 21.5, 61.1, 120.8, 122.5, 124.9, 125.6, 128.8, 129.9, 130.8, 134.0, 134.2, 136.6, 143.1, 153.5, 158.1, 165.9, 187.6; IR (KBr): ν 2306, 1708, 1110 cm^{-1}; GC–MS (m/z): 358 (3), 329 (100). Anal. Calcd for $C_{22}H_{18}N_2O_3$: C, 73.73; H, 5.06; N, 7.82. Found: C, 73.71; H, 5.04; N, 7.84.

4.6.5. Ethyl 7-formyl-2-phenyl-3-(trifluoromethyl)-2*H*-azuleno-[8,1-*cd*]pyridazine-5-carboxylate (9e)

Yield 86%; yellow-green solid (mp: 223–224 °C); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.41 (t, 3H, J=7.2 Hz), 4.37 (q, 2H, J=7.2 Hz), 5.85 (d, 1H, J=12.6 Hz), 6.59 (dd, 1H, J=1.5, 12.6 Hz), 7.39–7.54 (m, 6H), 8.08 (s, 1H), 9.18 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 14.3, 60.8, 115.6 (q, J=33.0 Hz), 117.8, 119.0, 121.5, 121.9, 125.7, 128.1, 129.5, 130.6, 131.9, 133.4, 137.0, 140.1 (q, J=288.0 Hz), 142.2, 150.1, 159.7, 164.9, 191.6; ^{19}F NMR (376.5 MHz, $CDCl_3$): δ −70.0; IR (KBr): ν 2318, 1702, 1114 cm^{-1}; GC–MS (m/z): 412 (100), 384 (39). Anal. Calcd for $C_{22}H_{15}F_3N_2O_3$: C, 64.08; H, 3.67; N, 6.79. Found: C, 64.10; H, 3.68; N, 6.78.

4.6.6. Ethyl 2-ethyl-4-formyl-2*H*-azuleno[8,1-*cd*]pyridazine-5-carboxylate (9f)

Yield 88%; green color viscous liquid; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.40 (t, 3H, J=7.2 Hz), 1.52 (q, 3H, J=7.2 Hz), 4.01 (q, 2H, J=7.5 Hz), 4.39 (q, 2H, J=6.9 Hz), 5.56 (dd, 1H, J=3.6, 8.1 Hz), 5.96 (dd, 1H, J=3.6, 8.1 Hz), 6.08 (dd, 1H, J=4.2, 8.1 Hz), 7.41 (d, 1H, J=11.7 Hz), 8.89 (s, 1H), 10.43 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 14.3, 14.9, 57.0, 60.5, 119.2, 122.1, 122.8, 124.9, 126.7, 129.0, 134.2, 135.4, 137.2, 140.4, 160.5, 165.2, 189.3; IR (KBr): ν 2316, 1705, 1104 cm^{-1}; LC–MS (m/z): 297 (M+1, 22.70), 309 (15.55), 319 (M+23, 100), 320 (19.92), 381 (21.78). Anal. Calcd for $C_{17}H_{16}N_2O_3$: C, 68.91; H, 5.44; N, 9.45. Found: C, 68.90; H, 5.44; N, 9.43.

4.6.7. Ethyl 4-formyl-2-(prop-1-en-2-yl)-2*H*-azuleno [8,1-*cd*]pyridazine-5-carboxylate (12)

Yield 82%; green solid (mp: 116–117 °C); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.39 (t, 3H, J=7.2 Hz), 2.23 (s, 3H), 4.37 (q, 2H, J=14.4 Hz), 5.08 (s, 1H), 5.52 (dd, 1H, J=8.1, 11.7 Hz), 5.58 (s, 1H), 5.92 (d, 1H, J=12.3 Hz), 6.04 (dd, 1H, J=8.1, 12.3 Hz), 7.33 (d, 1H, J=11.7 Hz), 8.99 (s, 1H), 10.39 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 14.3, 19.2, 60.7, 109.2, 120.5, 121.7, 123.3, 126.3, 127.0, 129.3, 134.0, 135.0, 137.2, 138.6, 146.1, 159.4, 165.1, 189.3; IR (KBr): ν 1680, 1110, 1057 cm^{-1}; GC–MS (m/z): 308 (95), 279 (100), 239 (56). Anal. Calcd for $C_{18}H_{16}N_2O_3$: C, 70.12; H, 5.23; N, 9.09. Found: C, 70.12; H, 5.20; N, 9.10.

4.6.8. Ethyl 2-(4-ethoxy-4-oxobut-2-en-2-yl)-4-formyl-2*H*-azulen-[8,1-*cd*]pyridazine-5-carboxylate (13)

Yield 78%; green solid (mp: 155–156 °C); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.34 (t, 3H, J=7.2 Hz), 1.42 (t, 3H, J=7.2 Hz), 2.67 (s, 3H), 4.26 (q, 2H, J=7.2 Hz), 4.41 (q, 2H, J=7.2 Hz), 5.60 (dd, 1H, J=8.1, 11.7 Hz), 5.98 (d, 1H, J=12.3 Hz), 6.10 (dd, 1H, J=8.1, 12.3 Hz), 6.52 (s, 1H), 7.35 (d, 1H, J=11.7 Hz), 9.10 (s, 1H), 10.45 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 14.1, 14.3, 15.6, 60.8, 60.9, 113.9, 121.5, 121.6, 123.8, 127.4, 127.9, 129.5, 134.1, 134.9, 137.5, 139.1, 153.6, 159.5, 164.9, 165.3, 189.3; IR (KBr): ν 1680, 1106, 1039 cm^{-1}; GC–MS (m/z): 380 (100), 351 (49), 239 (62). Anal. Calcd for $C_{21}H_{20}N_2O_5$: C, 66.31; H, 5.30; N, 7.36. Found: C, 66.31; H, 5.32; N, 7.35.

4.6.9. Ethyl 2-(4-ethoxy-4-oxobut-2-en-2-yl)-2*H*-azuleno[8,1-*cd*]-pyridazine-5-carboxylate (14)

Yield 85%; green solid (mp: 124–125 °C); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.28 (t, 3H, J=7.2 Hz), 1.33 (t, 3H, J=7.2 Hz), 2.54 (s, 3H), 4.18 (q, 2H, J=7.2 Hz), 4.26 (q, 2H, J=7.2 Hz), 5.35 (dd, 1H, J=8.0, 11.2 Hz), 5.73 (d, 1H, J=12.0 Hz), 5.87 (dd, 1H, J=8.0, 12.0 Hz), 6.47 (s, 1H), 7.09 (s, 1H), 7.28 (d, 1H, J=11.2 Hz), 7.83 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 14.2, 14.4, 14.8, 60.0, 60.5, 110.4, 115.9, 120.2, 122.9, 126.0, 126.4, 129.9, 132.9, 135.6, 137.0, 137.3, 152.4, 160.1, 165.5, 166.2; IR (KBr): ν 1672, 1109, 1052 cm^{-1}; GC–MS (m/z): 352 (100), 240 (40), 212 (60). Anal. Calcd for $C_{20}H_{20}N_2O_4$: C, 68.17; H, 5.72; N, 7.95. Found: C, 68.15; H, 5.71; N, 7.95.

4.7. Typical procedure for the preparation of compounds 17 and 19

To a solution of **16** or **18** (1 mmol) in ethanol (3 mL), was added NH_2NH_2 (1.2 mmol) at room temperature and the reaction continued at reflux temperature for 2 h, then the reaction mixture was allowed to cool to room temperature and diluted with water (10 mL) and extracted with EtOAc. The combined organic layers were dried over anhydrous $MgSO_4$, filtered, and stripped off solvent to give crude product, which was purified by silica gel column chromatography.

4.7.1. Ethyl 3-(2-hydroxypropyl)-1*H*-azuleno[8,1-*cd*]pyridazine-5-carboxylate (17)

Yield 75%; blue solid (mp: 201–202 °C); ^{1}H NMR (CD_3OD, 300 MHz): δ 1.23 (t, 3H, J=6.3 Hz), 1.37 (t, 3H, J=7.2 Hz), 2.56 (q, 1H, J=6.6 Hz), 2.69 (q, 1H, J=6.6 Hz), 4.20–4.34 (m, 3H), 4.80–4.50 (m, 2H), 5.78 (t, 1H, J=10.9 Hz), 6.01 (d, 1H, J=11.5 Hz), 6.51 (t, 1H, J=11.5 Hz), 7.13 (s, 1H), 7.97 (d, 1H, J=10.9 Hz); ^{13}C NMR (CD_3OD, 75 MHz): δ 13.4, 21.9, 41.5, 59.4, 65.0, 112.3, 117.7, 118.2, 118.4, 119.4, 128.3, 132.8, 138.5, 140.4, 152.0, 153.0, 166.5; IR (KBr): ν 3432, 3357, 1674, 1178, 1035 cm^{-1}; GC–MS (m/z): 298 (M^+, 100), 281 (12), 254 (30), 226 (31), 209 (20), 181 (24). Anal. Calcd for $C_{17}H_{18}N_2O_3$: C, 68.44; H, 6.08; N, 9.39. Found: C, 68.45; H, 6.09; N, 9.40.

4.7.2. Ethyl 3-(4-oxopentyl)-1*H*-azuleno[8,1-*cd*]pyridazine-5-carboxylate (19)

Yield 78%; blue solid (mp: 190–191 °C); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.39 (t, 3H, J=7.2 Hz), 1.94–2.05 (m, 2H), 2.13 (s, 3H), 2.50–2.58 (m, 4H), 4.35 (q, 2H, J=11.5 Hz), 5.80–5.94 (m, 2H), 6.52 (t, 1H, J=11.5 Hz), 7.19 (s, 1H), 8.14 (d, 1H, J=10.8 Hz); ^{13}C NMR

($CDCl_3$, 75 MHz): δ 14.5, 20.1, 30.0, 31.5, 42.8, 59.8, 113.4, 117.3, 117.6, 119.5, 120.1, 129.0, 133.2, 139.8, 141.0, 151.7, 154.7, 166.1, 208.8; IR (KBr): ν 3446, 1687, 1135, 1073, 1037 cm^{-1}; GC–MS (*m*/*z*): 324 (M^+, 91), 281 (50), 237 (11), 206 (100), 146 (13). Anal. Calcd for $C_{19}H_{20}N_2O_3$: C, 70.35; H, 6.21; N, 8.64. Found: C, 70.34; H, 6.23; N, 8.62.

4.8. Procedure for the preparation of compound 20

To a solution of ethyl 3-(4-oxopentyl)-1*H*-azuleno[8,1-*cd*]-pyridazine-5-carboxylate (19, 1 mmol) in EtOH (3 mL), was added *p*-TSA (1.2 mmol) at room temperature and refluxed at 100 °C for 2 h. Then the reaction mixture was allowed to cool to room temperature, and quenched with water and extracted with EtOAc. The combined organic layer was dried over anhydrous $MgSO_4$, filtered, and stripped off solvent to give crude product, which was purified by silica gel column chromatography to afford the compound 20. Yield 85%; blue solid (mp: 200–201 °C); ^1H NMR ($CDCl_3$, 300 MHz): δ 1.37 (t, 3H, *J*=7.2 Hz), 2.10 (s, 3H), 2.40 (t, 2H, *J*=6.9 Hz), 2.57 (t, 2H, *J*=6.9 Hz), 4.37 (q, 2H, *J*=7.2 Hz), 5.65–5.74 (m, 2H), 5.87 (t, 1H, *J*=11.7 Hz), 6.39 (m, 1H), 7.37 (d, 1H, *J*=10.9 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 14.3, 23.4, 25.1, 34.7, 60.9, 116.1, 116.9, 119.3, 121.0, 125.1, 127.3, 128.3, 132.0, 133.2, 137.5, 140.1, 151.1, 157.2, 168.6; IR (KBr): ν 3459, 1676, 1178, 1104, 1076 cm^{-1}; GC–MS (*m*/*z*): 306 (M^+, 94), 263 (29), 207 (100), 177 (7), 147 (13). Anal. Calcd for $C_{19}H_{18}N_2O_2$: C, 74.49; H, 5.92; N, 9.14. Found: C, 74.50; H, 5.93; N, 9.12.

4.9. Procedure for the preparation of ethyl 3-(4-hydroxypentyl)-*1H*-azuleno[8,1-*cd*]pyridazine-5-carboxylate (21)

To a solution of ethyl 3-(4-oxopentyl)-1*H*-azuleno[8,1-*cd*]-pyridazine-5-carboxylate (**19**, 1 mmol) in EtOH (3 mL), was added $NaBH_4$ (1.2 mmol) at room temperature and heated at 50 °C for 40 min. Then the reaction mixture was allowed to cool to room temperature, and quenched with water (10 mL) and extracted with EtOAc. The combined organic layer was dried over anhydrous $MgSO_4$, filtered, and stripped off solvent to give crude product, which was purified by silica gel column chromatography to afford the compound **21**. Yield 95%; blue solid (mp: 195–196 °C); ^1H NMR (CD_3OD, 300 MHz): δ 1.14 (d, 3H, *J*=6.0 Hz), 1.36 (t, 3H, *J*=6.9 Hz), 1.50–1.55 (m, 2H), 1.67–1.86 (m, 2H), 2.46 (t, 2H, *J*=7.5 Hz), 3.70–3.80 (m, 1H), 4.30 (q, 2H, *J*=6.9 Hz), 4.61 (s, 1H), 5.75–5.82 (m, 1H), 6.00 (d, 1H, *J*=11.7 Hz), 6.47–6.54 (m, 1H), 7.11 (s, 1H), 7.97 (d, 1H, *J*=10.9 Hz); ^{13}C NMR (CD_3OD, 75 MHz): δ 13.5, 22.1, 22.5, 32.0, 38.4, 59.4, 66.8, 112.2, 117.6, 117.7, 118.3, 119.4, 128.3, 132.7, 138.5, 140.3, 152.2, 155.4, 166.6; IR (KBr): ν 3330, 1667, 1184, 1080, 1031 cm^{-1}; GC–MS (*m*/*z*): 326 (M^+, 93), 207 (100), 185 (24), 147 (14). Anal. Calcd for $C_{19}H_{22}N_2O_3$: C, 69.92; H, 6.79; N, 8.58. Found: C, 69.91; H, 6.80; N, 8.59.

4.10. Procedure for the preparation of 22a and 22b

Similar to the general procedure of Section 4.3.

4.10.1. Ethyl 4-(3-oxobutyl)-1*H*-azuleno[8,1-*cd*]pyridazine-5-carboxylate (22a)

Yield 47%; green solid (mp: 138–139 °C); ^1H NMR ($CDCl_3$, 300 MHz): δ 1.34 (t, 3H, *J*=7.2 Hz), 2.06 (s, 3H), 2.68 (t, 2H, *J*=7.2 Hz), 3.08 (t, 2H, *J*=7.2 Hz), 4.29 (q, 2H, *J*=7.2 Hz), 5.65 (dd, 1H, *J*=8.8, 11.0 Hz), 5.74 (d, 1H, *J*=11.6 Hz), 6.32 (dd, 1H, *J*=8.8, 11.6 Hz), 7.70 (s, 1H), 7.86 (d, 1H, *J*=11.0 Hz), 10.19 (br s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 14.4, 20.9, 30.1, 44.7, 59.8, 116.8, 117.0, 117.5, 120.1, 128.6, 129.2, 133.5, 139.8, 141.0, 143.6, 152.7, 166.4, 209.6; IR (KBr): ν 2300, 1690, 1480 cm^{-1}; GC–MS (*m*/*z*): 310 (110), 253 (61), 221 (76). Anal. Calcd for $C_{18}H_{18}N_2O_3$: C, 69.66; H, 5.85; N, 9.03. Found: C, 69.64; H, 5.83; N, 9.00.

4.10.1.1. Crystal data for ***22a****.* Empirical formula=$C_{18}H_{18}N_2O_3$; formula weight=310.34; temperature=295 (2) K; wavelength=0.71073 Å; crystal system=monoclinic; space group=*C*2/*c*; unit cell dimensions, *a*=15.9841 (17) Å; *b*=16.5867 (18) Å; *c*=13.1061 (14) Å; α=90°; β=116.264 (3)°; γ=90°; volume=3116.0 (6) $Å^3$; *Z*=8; density (calculated)=1.323 Mg/m^3; absorption coefficient=0.091 mm^{-1}; *F*(000)=1312; crystal size=0.15×0.15×0.04 mm^3; theta range for data collection=1.88–28.36°; index ranges=$-21\le h\le 14$, $-20\le k\le 22$, $-17\le l\le 16$; reflections collected=14,020; independent reflections=3897 [*R*(int)=0.0644]; completeness to theta=28.36°=99.7%; absorption correction=semi-empirical from equivalents; max. and min. transmission=0.9964 and 0.9865; refinement method=full-matrix least-squares on F^2; data/restraints/parameters=3897/0/208; goodness-of-fit on F^2=0.980; Final *R* indices [*I*>2sigma(*I*)]=*R*1=0.0584, *wR*2=0.1226; *R* indices (all data)=*R*1=0.1601, *wR*2=0.1574; largest diff. peak and hole=0.209 and −0.246 e $Å^{-3}$. Detailed X-ray crystallographic data is available from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK (for compound **22a** CCDC # 844734).

4.10.2. Ethyl 2,4-bis(3-oxobutyl)-2*H*-azuleno[8,1-*cd*]pyridazine-5-carboxylate (22b)

Yield 23%; green solid (mp: 138–139 °C); ^1H NMR ($CDCl_3$, 300 MHz): δ 1.29 (t, 3H, *J*=7.2 Hz), 2.00 (s, 3H), 2.13 (s, 3H), 2.64 (t, 2H, *J*=6.0 Hz), 2.90–2.98 (m, 4H), 3.83 (t, 2H, *J*=6.0 Hz), 4.23 (q, 2H, *J*=7.2 Hz), 5.13 (dd, 1H, *J*=8.2, 11.4 Hz), 5.47 (d, 1H, *J*=12.3 Hz), 5.72 (dd, 1H, *J*=8.2, 12.3 Hz), 7.15 (d, 1H, *J*=11.4 Hz), 7.75 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 14.3, 20.3, 30.1, 30.2, 41.4, 44.8, 54.7, 59.7, 119.1, 120.3, 120.7, 124.3, 126.4, 128.9, 132.8, 136.7, 137.2, 141.0, 161.8, 166.3, 205.5, 209.0; IR (KBr): ν 2320, 1702, 1490, 1476, 1180 cm^{-1}; GC–MS (*m*/*z*): 380 (100), 302 (58). Anal. Calcd for $C_{22}H_{24}N_2O_4$: C, 69.46; H, 6.36; N, 7.36. Found: C, 69.48; H, 6.35; N, 7.38.

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Supplementary data

Copies of ^1H NMR, ^{13}C NMR, DEPT, and ^{19}F NMR spectra are available. Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.tet.2013.04.034.

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10. Detailed X-ray crystallographic data are available from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; for the compounds **5b**, **7d**, **7f**, **8b** and **22a** (CCDC #882109; 887649; 887650; 844733; 844734).